

**Novel benzyne insertion reactions
&
Medium-ring synthesis
by oxidative C-H coupling**



A thesis submitted for the degree of
Doctor of Philosophy in
Organic Chemistry
Edinburgh University - 2011

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Declaration

I hereby declare that all of the work in this thesis is my own unless otherwise stated. This thesis contains no material which has been accepted for the award of any other degree or diploma in any University and fulfils the requirements for the degree of Doctor of Philosophy at the University of Edinburgh.

Didier G. Pintori

Acknowledgements

Firstly I would like to thank my supervisor Dr. Michael F. Greaney for giving me the opportunity to conduct this research in his laboratories. I would like to thank him for his advice, guidance and support over the last three years as well as his continuous support of my ideas. I would like to thank everyone in the Greaney group, especially Dr. Stephan A. Ohnmacht, Naim Nazef and Kallol Biswas as well as all the guys who supported my research in any way.

I would also like to thank the French crew (Nicolas Petitjean, Aline Devoille, Géraldine Escher, Yan Jauffret, Marine Raman and Anne-Frédérique Pécharman) for all the good food we cooked.

A huge thank you goes to all the support staff at the Edinburgh University, especially Marika de Cremoux and Juraj Bella for their help with NMR; Raymond Borwick, Tim Calder, Derek Burgess and John Knox for their help with ordering stuff.

I also would like to thank the University of Edinburgh and the School of Chemistry for providing the facilities, the Swansea EPSRC National Mass Spectrometry Service Centre at the University of Wales for analytical data as well as EaStCHEM for funding.

I would like to thank my mum, dad and sisters who always offered continued support and encouragement. Finally, a heartfelt thanks goes out to my girlfriend, Marie, for all your love, support and patience when I was only thinking about strange molecules. Thank you for sharing both good times and bad, for keeping me smiling and making me very happy!

Didier Pintori

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Preface

Parts of this thesis have been communicated in the literature and have been co-written by the author of this thesis:

“Insertion of benzene rings into the amide bond, one-step synthesis of acridines and acridones from aryl amides” Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168-171

“Intramolecular oxidative C-H coupling for medium ring synthesis” Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2011**, *133*, 1209-1211

Abbreviations

General

| | |
|----------|---|
| Atm | Atmosphere |
| cald. | Calculated |
| CMD | Concerted metalation-deprotonation |
| CNS | Central nervous system |
| δ | Chemical shift |
| d | Doublet |
| EDG | Electron-donating group |
| equiv | Equivalent(s) |
| ES | Electrospray ionization |
| EWG | Electron-withdrawing group |
| h/hrs | Hour(s) |
| HPLC | High performance liquid chromatography |
| HRMS | High resolution mass spectrometry |
| Hz | Hertz |
| IR | Infrared |
| J | Coupling constant |
| KIE | Kinetic isotope effect |
| LCMS | Liquid chromatography-mass spectrometry |
| LUMO | Lowest unoccupied molecular orbital |
| M | Metal/metalloid |
| m | Multiplet (spectral) |
| m/z | Mass to charge ratio |
| M+ | Parent molecular ion |
| mDRC | mitochondrial diazepam receptor complex |
| mL | Millilitre |
| mmol | Millimoles |
| MW | Microwave |
| NMR | Nuclear magnetic resonance |
| o/n | Overnight |

| | |
|-------------------|------------------------------------|
| OLED | Organic light emitting diode |
| ppm | Parts per million |
| q | Quartet (spectral) |
| R.T. | Room temperature |
| s | Singlet (spectral) |
| S _E Ar | Substitution electrophile aromatic |
| S _N Ar | Substitution nucleophilic aromatic |
| t | Triplet (spectral) |
| TCC | Three-component cross-coupling |
| TLC | Thin layer chromatography |
| UV | Ultra violet |
| °C | Degree(s) Celsius |
| μL | Microlitre |

Reagents and Solvents

| | |
|----------------------|--------------------------------------|
| Bipy | 2,2-Bipyridine |
| BQ | 1,4-Benzoquinone |
| CsF | Caesium fluoride |
| Cu(OAc) ₂ | Copper acetate |
| DCE | Dichloroethane |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichloro-5,6-dicyanobenzoquinone |
| DMA | <i>N,N</i> -dimethylacetamide |
| DME | 1,2-Dimethoxyethane |
| DMF | <i>N,N</i> -dimethylformamide |
| DMSO | Dimethylsulfoxide |
| Et ₂ O | Diethyl ether |
| EtOAc | Ethyl acetate |
| HBP | Hermann-Beller palladacycle |
| HMDS | Hexamethyldisilazane |
| HPMV | Heteropolymolybdovanadic acid |
| IBX | 2-iodoxybenzoic acid |

| | |
|----------------------|--|
| KF | Potassium fluoride |
| LDA | Lithium diisopropylamine |
| MeCN | Acetonitrile |
| NMP | <i>N</i> -methyl-2-pyrrolidione |
| Pd(OAc) ₂ | Palladium acetate |
| Pd(TFA) ₂ | Palladium trifluoroacetate |
| PdCl ₂ | Palladium chloride |
| PivOH | Pivalic acid |
| Py | Pyridine |
| TBAF | Tetrabutylammonium fluoride |
| TBAT | Tetrabutylammonium difluorotriphenylsilicate |
| TBHP | <i>tert</i> -Butyl hydroperoxide |
| TBP | Di- <i>tert</i> -butyl peroxide |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TMSBr | Trimethylsilyl bromide |
| Tol | Toluene |

Substituents and Protecting groups

| | |
|--------------|-------------------------------|
| Ac | Acetyl |
| Ar | Aryl |
| Bn | Benzyl |
| Boc | <i>tert</i> -Butyloxycarbonyl |
| CBz | Carbobenzyloxy |
| Cy | Cyclohexyl |
| Fmoc | 9-Fluorenylmethyloxycarbonyl |
| <i>i</i> -Pr | <i>iso</i> -Propyl |
| MOM | Methoxymethyl ether |
| Ms | Mesyl |
| Piv | Pivaloyl |
| TMS | Trimethylsilyl |
| Ts | Tosyl |

Abstract

This thesis is divided into two main chapters, which are focused on two separated and uncorrelated research areas. The first part of this thesis is dedicated to the research I carried out in benzyne chemistry and the second part is focused on catalytic C-H bond activation.

In the first place, a novel insertion reaction of arynes into the nitrogen-carbonyl σ -bond of amides has been investigated as a rapid and powerful approach for the preparation of valuable *ortho*-disubstituted arenes. Readily available aromatic amides undergo smooth insertion when treated with *O*-triflatophenyl silane aryne precursors, producing versatile anthranilic derivatives in good to excellent yields. The process is entirely metal-free and has been expanded to the synthesis of biologically active heterocycles such as acridones and acridines.

Secondly, the synthesis of medium-sized ring systems by intramolecular oxidative C-H bond coupling has been explored.

Despite the abundance of biologically active natural products featuring medium-sized rings, the synthesis of such ring systems using classical synthetic routes faces many challenges and has led to a dearth of medium ring compounds in medicinal chemistry. In contrast to the more facile 5-membered ring synthesis by oxidative C-H coupling, medium ring synthesis has not been previously reported using this approach. The chemistry, which requires zero pre-functionalisation of the substrates, is catalysed by palladium and has been exemplified using heteroaromatic substrates at the core of numerous biologically active molecules. The mechanism of the reaction has also been studied and a catalytic cycle has been proposed

CHAPTER 1

Novel benzyne insertion reactions

1.1 Introduction to benzyne's chemistry

Benzyne chemistry is known for more than hundred years and has been extensively reviewed over the past decades;¹⁻⁶ the following introduction will be an update of *ortho*-aryne chemistry published in the last four years (2006-2010).

This section of this thesis will be mainly focused on the recent developments made regarding the insertion reactions of arynes into element-element sigma bonds. Related benzyne transformations such as pericyclic reactions, ene reactions, addition reactions and transition-metal catalysed reactions will not be discussed in this introduction as they are not fully relevant to the topic of this thesis.

Nevertheless, an overview of general aspects about the structure, the reactivity, and the main methods for the generation of arynes will be given in the first place and the rest of the introduction will be devoted to the more recent advances in insertion reactions of arynes into element – element bonds.

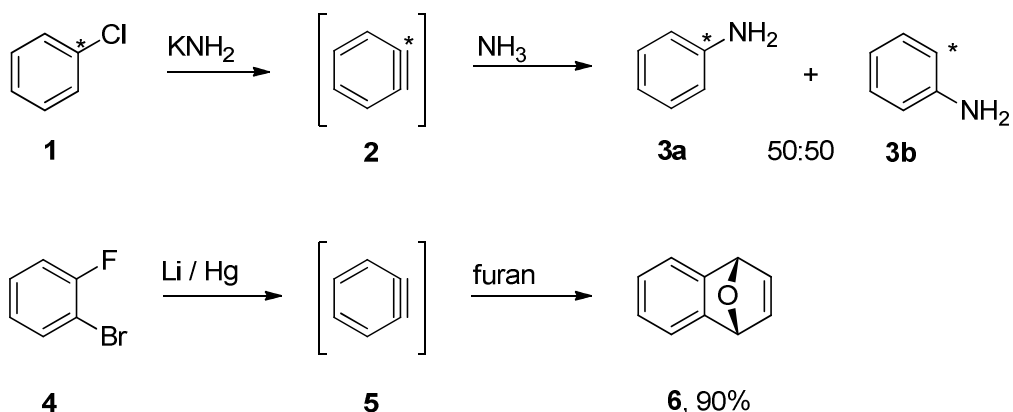
1.1.1 Structure, reactivity and generation of arynes

1.1.1.1 Structure and reactivity of benzyne

Arynes and heteroarynes are neutral, reactive, aromatic intermediates lacking two adjacent hydrogen atoms on an aromatic ring. Thus, *ortho*-benzyne or 1,2 di-dehydrobenzene has two atomic orbitals perpendicular to the aromatic π system forming a weakly bonding molecular orbital occupied by two electrons which enhances its reactivity.

The first evidence for the production of such reactive aromatic intermediates was postulated over 100 years ago, by Stoermer and Kahlert in 1902⁷ and it took twenty five years for Bachmann and Clarke at the laboratory of Eastman Kodak company to propose the structure of the symmetrical intermediate benzyne.⁸

However, it is probably Roberts' radiolabeled experiments with the reaction of ¹⁴C-labeled chlorobenzene **1** with potassium amide⁹ and the Diels-Alder trapping reaction carried out by Wittig¹⁰ in the 1950's that gave the first strong support of the existence of benzyne. (Scheme 1.1)



Scheme 1.1 Roberts' radiolabeled experiment and Wittig's Diels-Alder trapping reaction

Over the past 50 years following the first identification of benzyne, scientists have been able to use spectroscopic methods such as UV, NMR and IR to observe benzyne directly and this, along with theoretical calculations, have given researchers a wider insight into its nature. Benzyne is commonly represented by a triple bond **5** although a number of different structures, for instance a diradical **7** or a zwitterion **8**, have been proposed. (Figure 1.1)

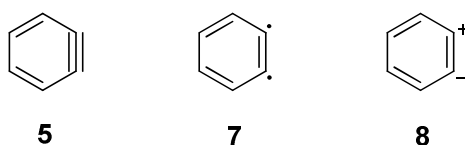


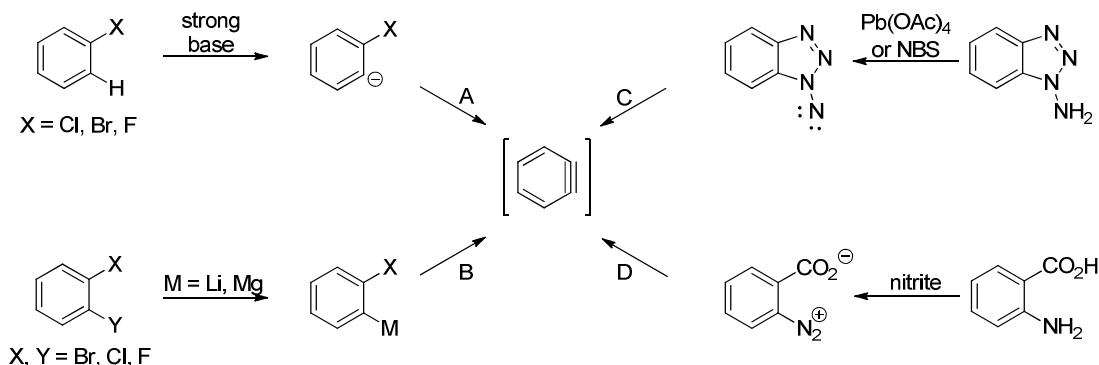
Figure 1.1. Proposed representations of benzyne

Studies of benzyne by infrared spectroscopy have shown that the triple bond generated is different from the triple bond of classic alkyne. In fact, one the π bonds belongs to the aromatic system whereas the other one is formed by lateral overlap of the two sp^2 orbitals in the plane of the ring. Though it has similar characteristics to alkynes, the benzyne triple bond is highly strained and more reactive.¹¹ A direct consequence of the strained nature of the ring is that arynes have low lying LUMOs and *ortho*-benzyne can participate in a wide range of reactions. As a matter of fact, arynes can be involved in cycloaddition and ene reactions, behave as powerful electrophiles and eventually can be stabilised by complexation to transition-metals.

1.1.1.2 Generation of benzyne

Over the past decades the use of benzyne in synthesis has grown, illustrated in particular by its use in a number of renowned natural products syntheses.^{6,12,13} As a reactive intermediate benzyne cannot be stored or handled as isolated species, it must be generated *in situ*. Two aspects are said to be important in the methods of benzyne generation. Firstly, the intermediate benzyne must be generated in high yields and secondly the rate of its generation must be carefully controlled in order to avoid any side reactions which could be found when benzyne is present in large concentrations. Along with classical techniques for its production, such as that employed by Roberts *et al.*, there has been significant research into novel methods of generating arynes.

Some of the earliest methods of generation of arynes required very harsh conditions. Synthetic routes involving strong bases, harsh oxidants, reducing metals or zwitterions meant that the chemistry compatible with benzyne generation was rather limited (Scheme 1.2).



Scheme 1.2. A summary of the traditional methods of benzyne generation

Thus, an aromatic halide can be treated with a strong base such as a potassium or sodium amide to remove the *ortho*-aromatic proton and generate benzyne *via* the elimination of an anion (path A). The use of such strong bases is problematic because these bases are most often nucleophilic enough to add onto benzyne and thus products obtained are those from the addition of the base. Indeed, as previously

mentioned in scheme 1.1, aniline is formed when sodium amide in liquid ammonia is used.

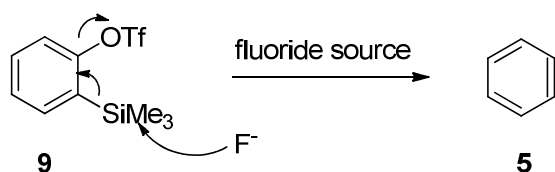
An alternative route is to use 1,2-dihalogenosubstituted benzene as starting materials (path B). Reaction with lithium or magnesium metal results in metal-halogen exchange generating a metal-halide species which produces the benzyne intermediate *via* an elimination reaction.¹⁴ Despite the latest improvements and variations of this technique of benzyne generation,¹⁵⁻¹⁷ the use of organometallic species is still not fully compatible with substrates containing sensitive functional groups.

In 1963, Rees reported a very different approach for the generation of arynes, which involved the use of aminobenzotriazoles as benzyne precursors (path C).¹⁸⁻²⁰ Reaction with an oxidising agent, such as lead tetraacetate or *N*-bromosuccinimide results in the formation of a nitrene intermediate, which undergoes decomposition to yield benzyne and two equivalents of nitrogen gas. Alternative heterocycles and different oxidizing agents have been recently examined to assess how they affect the rate of benzyne formation. For instance, it has been found that iodobenzene diacetate could be used in the reaction and generated benzyne at a much slower rate.^{21,22}

Although many of the classical methods of generation are conducted at low temperature, benzyne can also be generated at elevated temperature through decomposition of zwitterionic species. The most well known example is the use of benzenediazonium-2-carboxylate, which in turn is generated *in situ* from anthranilic acid (path D).²³ Indeed, anthranilic acid in presence of an alkyl nitrite, typically *t*-butyl nitrite, generates the diazonium salt and leads to an elegant elimination of carbon dioxide and nitrogen to yield benzyne.

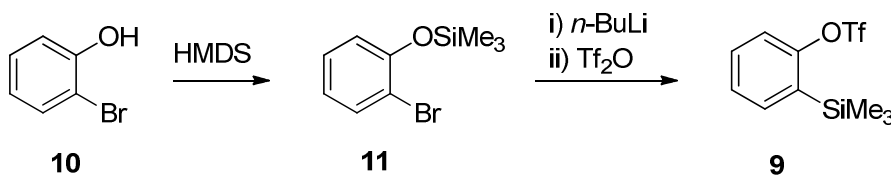
The necessity of harsh conditions in all the methods exposed above meant that the exploration of benzyne chemistry has traditionally been limited. However, the publication of work towards a novel method of benzyne generation under very mild conditions by Kobayashi in 1983 has led to a veritable renaissance of benzyne chemistry.

In fact, Kobayashi and co-workers detailed the fluoride-induced 1,2-elimination of *ortho*-trimethylsilylphenyl triflate **9** to generate benzyne (Scheme 1.3).^{24,25} Several fluoride sources such as caesium, potassium or tetrabutylammonium fluorides in combination with a large variety of solvents can be employed to give good yields in trapping experiments with furan. The concept of using *ortho*-substituted silylarene as benzyne precursor originally came from Cucino *et al.* who attempted to use an *ortho*-halo or *ortho*-tosyl group instead of a triflate to generate benzyne.²⁶ However, halo and tosyl moieties proved to be poor leaving groups, leading to unsatisfactory yields of benzyne and fast protonation of the desilylated anionic intermediate. Thus, the substitution of these poor leaving groups by a triflate group gave better yields of benzyne.



Scheme 1.3. Benzyne generation from *ortho*-trimethylsilylphenyl triflate **9**²⁴

Commercially available 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **9** is a stable liquid that can easily be prepared in large scale from *ortho*-bromophenol **10** (Scheme 1.4). A wide variety of substituted aryne precursors, incorporating electron-donating, -withdrawing and bulky substituents, have been synthesised using similar procedures²⁷⁻²⁹ and this methodology has also been extended to the generation of heteroarynes, such as 2,3- and 3,4-pyridine.^{30,31}



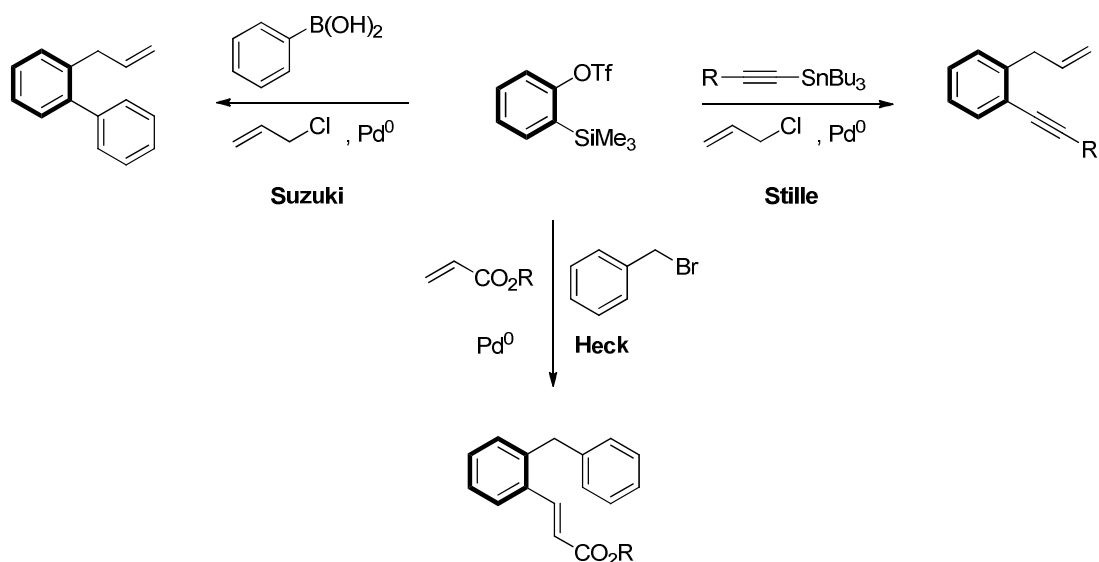
Scheme 1.4. Synthesis of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **9**

This last method of generation of arynes is in stark contrast to the traditional methods. It has served to make aryne chemistry more accessible, but crucially, it has allowed the combination of previously conflicting chemistries.

1.1.2 Insertion reactions of arynes

Arynes are powerful electrophiles and are most commonly used in nucleophilic additions and pericyclic reactions.^{32,33} Development of milder methods of benzyne generation, especially the use of silylaryl triflate as benzyne precursors has allowed to improve reaction conditions for both nucleophilic addition and pericyclic reactions.^{3,6,12}

Moreover, the use of such versatile benzyne precursors allowed organic chemists from the late 90's to study the possibility of incorporating arynes into transition metal catalysed reactions. Early work in this direction focused on the trimerisation of arynes to make triphenylenes.³⁴⁻³⁶ Later, three-component cross-coupling reactions (TCC) such as Stille,³⁷ Suzuki^{38,39} and Heck^{40,41} cross-coupling reactions have been reported and permitted the rapid synthesis of highly valuable *ortho*-disubstituted arenes (Scheme 1.5).



Scheme 1.5. Three component cross-coupling reactions with arynes

Ortho-disubstituted arenes are very precious building blocks for medicinal chemistry and organic chemists have found that such frameworks could easily be prepared without using any transition-metal by addition of element-element σ -bonds across the triple bond of arynes.

Commonly, the process occurs *via* addition of a nucleophile species **X** to benzyne leading to the formation of a carbanionic intermediate, which is then trapped by an electrophile **Y**. In the case where **X** and **Y** belong to the same molecule and are separated by a σ -bond, the reaction is usually the formal insertion of the aryne into the **X-Y** bond, creating two new carbon-element bonds (Figure 1.2).

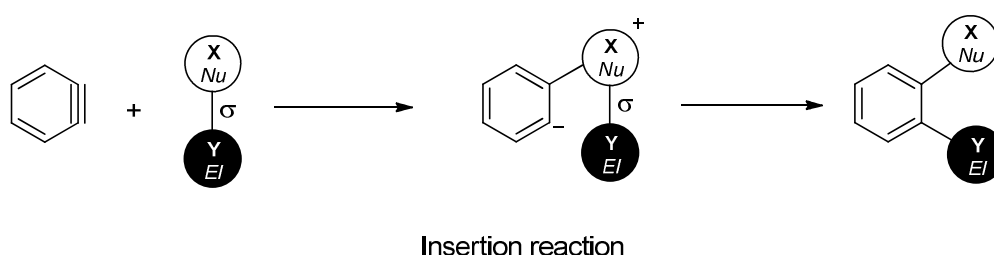


Figure 1.2. Insertion reaction of arynes

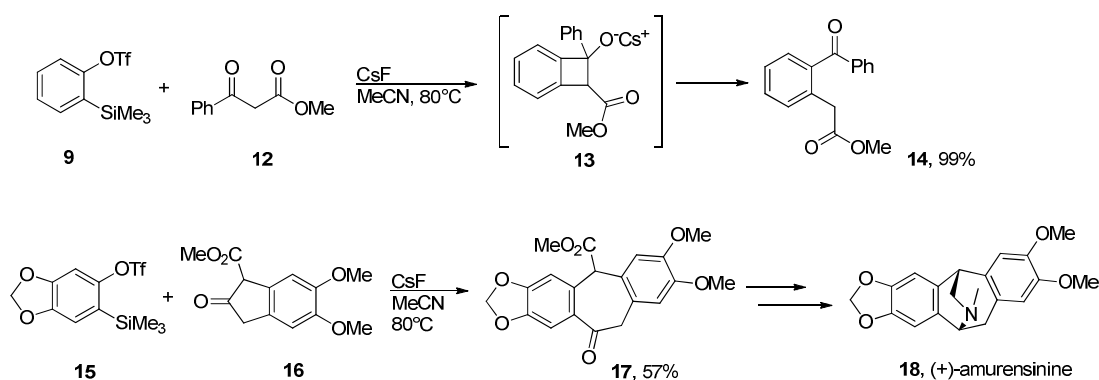
Insertion of arynes into σ -bond has been importantly reviewed in the past and catalytic σ -bond insertion reactions as well as heteroatom-metal, carbon-carbon and carbon-heteroatom insertion reactions are well documented.⁴²⁻⁴⁴

The latest general review of benzyne insertion has been published by Peña *et al.* in 2006⁴³ and in 2010 Yoshida and co-workers have also reviewed their own contribution to the topic.⁴⁴ As a result, the following section will be dedicated to the most recent examples of aryne σ -insertion published since 2006 and will be divided according to the nature of the σ -bond cleaved.

1.1.2.1 Carbon – carbon σ -bond

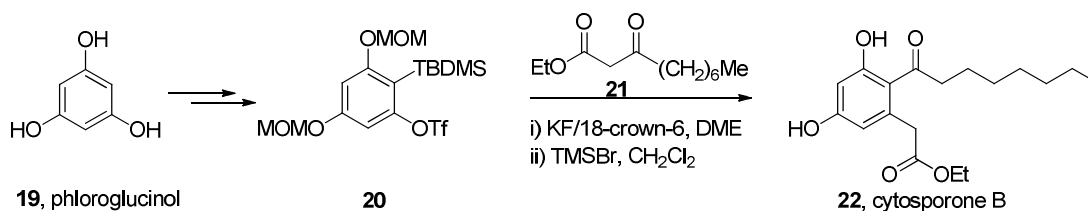
The addition of carbon-carbon bonds to benzyne proved to be a popular technique for the creation of multiple new carbon-carbon bonds in a single step and has been applied to the synthesis of several natural products.

Yoshida *et al.* and Stoltz *et al.* demonstrated that arynes can be inserted into the carbon-carbon bond of β -ketoesters and 1,3-diketones.^{42,43} CsF and KF simultaneously employed as fluoride source and base were used to generate benzyne and the active anionic species in solution. The authors suggested that the anion created adds to benzyne presumably by a formal [2 + 2] cycloaddition mechanism and the cyclobutane ring obtained rearranges to generate the observed products. The reaction was applicable to both cyclic and acyclic substrates and has been applied to the efficient construction of the carbon skeleton of amurensine **18** (Scheme 1.6).^{45,46}



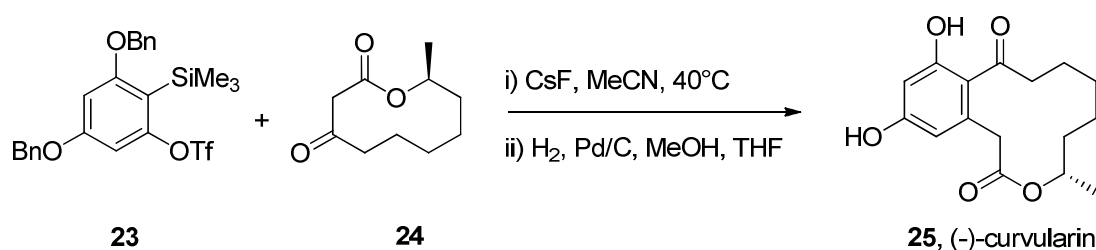
Scheme 1.6. Insertion of benzyne into carbon-carbon bond

More recently, cytosporone B (**22**), an octaketide metabolite with potential anti-cancer and anti-hypoglycaemia properties has been synthesised by Yoshida.⁴⁷ 3,5-bis(methoxymethoxy)benzyne precursor **20** produced from readily available 1,3,5-trihydroxybenzene **19** was found to be inserted in a regioselective manner into the active methylene-ketone carbonyl σ -bond of ethyl 3-oxodecanoate **21**. Deprotection of the resulting inserted product using TMSBr afforded the desired product. Cytosporone B was obtained in six steps and 16% overall yield based on phloroglucinol **19** (Scheme 1.7).



Scheme 1.7. Synthesis of cytosporone B by aryne carbon-carbon σ -bond insertion

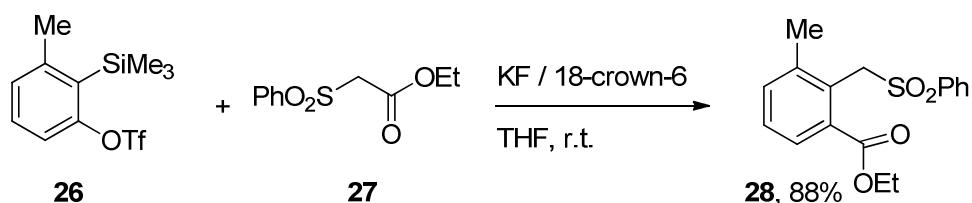
In 2010, Stoltz *et al.* also described the use of aryne σ -bond insertion for the synthesis of benzannulated macrolactone natural products.⁴⁸ Synthetically challenging 12-membered medium-sized lactone, (-)-Curvularin **25**, was successfully prepared from simple dipiodialide **24**, albeit in a modest 30% yield (Scheme 1.8).



Scheme 1.8. Synthesis of (-)-curvularin by aryne carbon-carbon σ -bond insertion

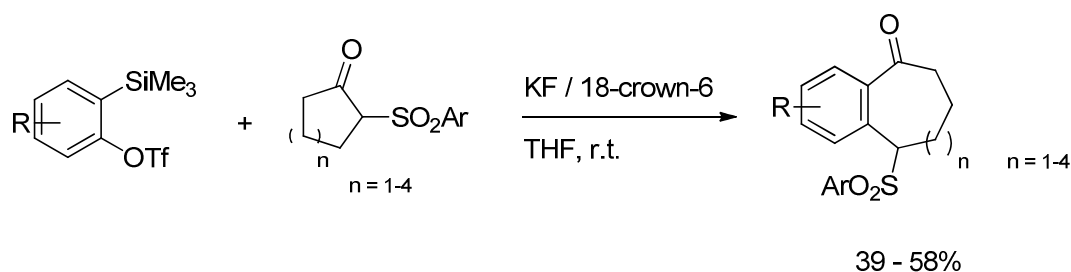
Similarly, insertion reactions into β -keto-sulfone, sulfonylacetonitrile and malononitrile derivatives have also been reported.

Huang and co-workers developed the novel addition of β -keto sulfones to the triple bond of arynes to prepare *ortho*-keto benzyl sulfones.⁴⁹⁻⁵¹ As in the insertion of 1,3-diketones, potassium fluoride was used as fluoride source and as a base for the benzyne generation as well as for the abstraction of the most acidic proton of the organosulfones. The anionic species generated after deprotonation reacted with the aryne intermediate creating a cyclobutane species, which rapidly rearranged to provide the disubstituted aromatic product in high yield (Scheme 1.9).

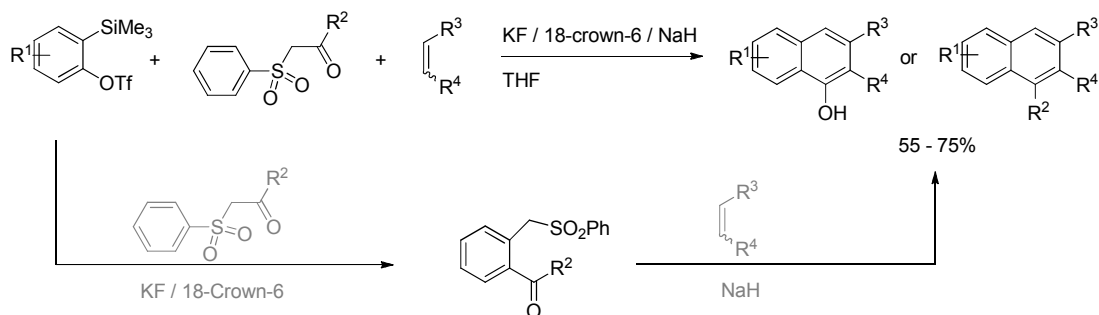


Scheme 1.9. Insertion of arynes into β -keto sulfones

The methodology has been extended to the syntheses of medium-sized ring systems (Scheme 1.10)⁵² and to the development of multicomponent reactions.⁴⁹ Huang *et al.* surprisingly found that polysubstituted naphthols and naphthalenes could be obtained in moderate yields by a novel three-component reaction of arynes, β -keto sulfones, and Michael-type acceptors. The reaction is very powerful as it permitted the formation of four new carbon-carbon bonds within one operation (Scheme 1.11).

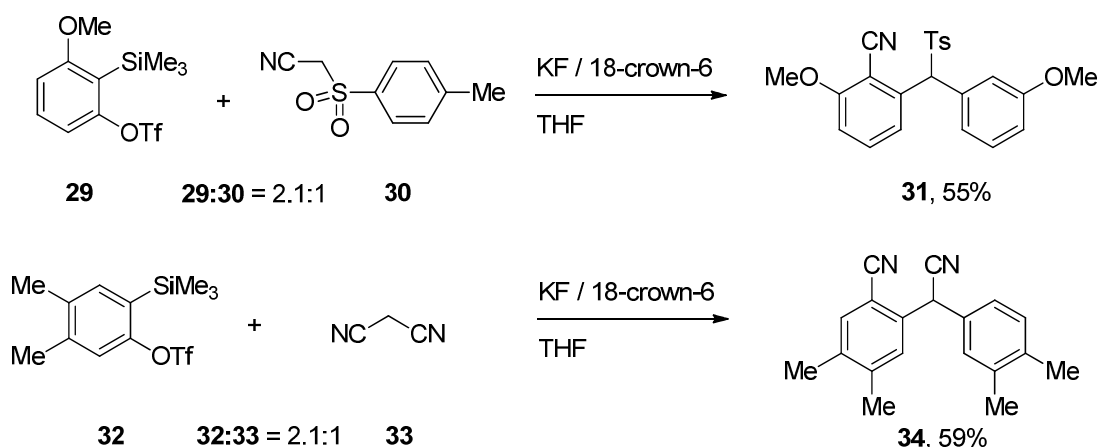


Scheme 1.10. Ring expansion reaction of β -sulfonyl cyclic ketones *via* insertion of arynes.



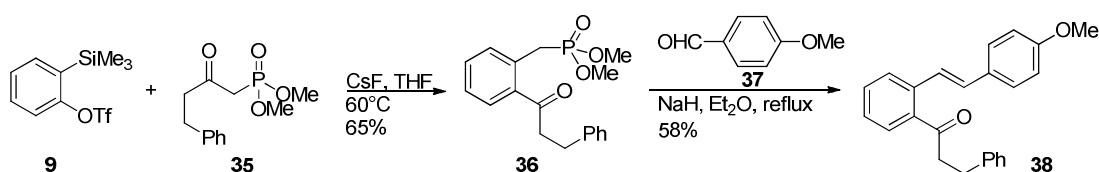
Scheme 1.11. Multicomponent reaction of aryne, β -keto sulfones, and Michael-type acceptors.

Similarly to the work presented above and to their prior work on the insertion of arynes into α -cyanocarbonyl compounds,⁵³ Yoshida and co-workers worked on the insertion of arynes into the methylene carbon-cyano carbon bond of *p*-tolylsulfonylacetonitrile.⁵⁴ In this example, the authors used an excess of benzyne precursor to create three new carbon-carbon and one carbon-hydrogen bonds all in one pot. Good regioselectivity was observed for the insertion of methoxybenzyne **29** and the scope of this methodology could be extended to malonitrile **33** (Scheme 1.12).



Scheme 1.12. Coupling reaction of arynes with *p*-tolylsulfonylacetonitrile **30** and malononitrile **33**.

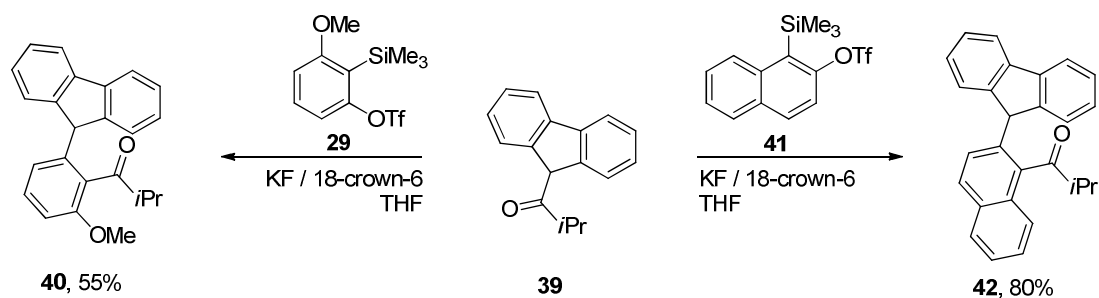
In 2009, the same type of transformation has been applied to activated β -ketophosphonates as well as acylbenzylphosphonates. The reaction enable the synthesis of precursors for the Wittig reactions (Scheme 1.13).⁵⁵ This reaction differed from the one published by Yoshida and Kunai in 2005, where the reaction of carbophosphinylation afforded a new carbon-carbon and carbon-phosphorus bonds.⁵⁶



Scheme 1.13. Insertion reaction into β -ketophosphonate **35**.

The key of such successful insertion reaction is the fast generation of a carbanionic species *via* rapid deprotonation promoted by two adjacent electron-withdrawing groups. Thus, this pushed chemists to investigate other molecular scaffolds having C-H bonds of suitable acidity for the development of new C-C cleavage reactions using arynes.

9-fluorenyl ketones were ideal substrates and led to facile insertion into the methine-carbonyl bond to give the acylfluorenylation product.⁵⁷ In this case, aromatic stabilisation of the carbanionic species allowed two carbon-carbon bonds to be formed. A variety of fluorenyl ketones and esters were easily added to arynes and once again, good regioselectivities were observed in the reaction of 1,2-naphthalene **41** or 3-methoxybenzyne **29**, where the fluorenyl moiety (nucleophilic site) was exclusively connected to the less congested site (Scheme 1.14).



Scheme 1.14. Acylfluorenylation of arynes.

Similar to the insertion of arynes into C-C σ -bonds discussed above, carbon-halogen, carbon-oxygen and carbon-nitrogen bonds were thought to be targets of choice for the rapid and smooth entry to valuable heteroaromatic scaffolds and building blocs.

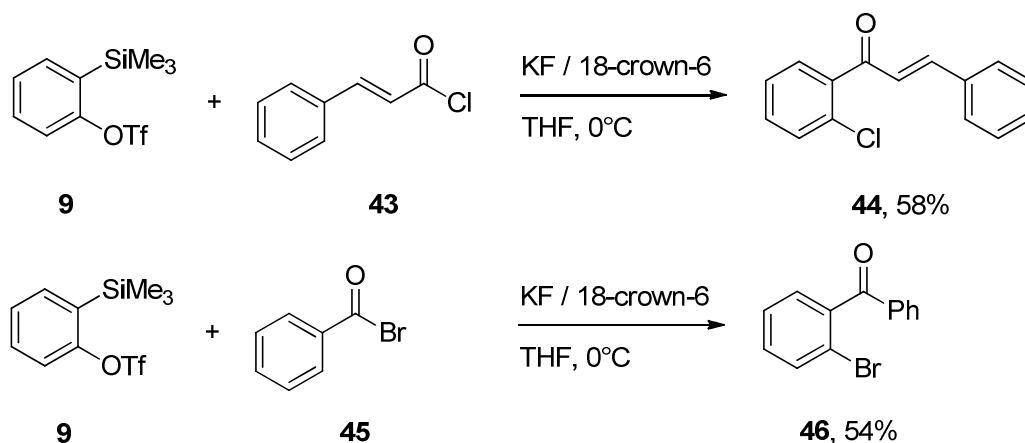
1.1.2.2 Carbon-halogen σ -bond

The electrophilicity of arynes enables even halogen moieties to behave as nucleophilic sites in the insertion reaction.

In 2007, Yoshida *et al.* reported the smooth insertion of arynes into a chlorine-carbonyl σ -bond.⁵⁸ The reaction of benzyne with benzoyl chloride derivatives gave yields of inserted products up to 70%. The chemistry proved to be highly compatible

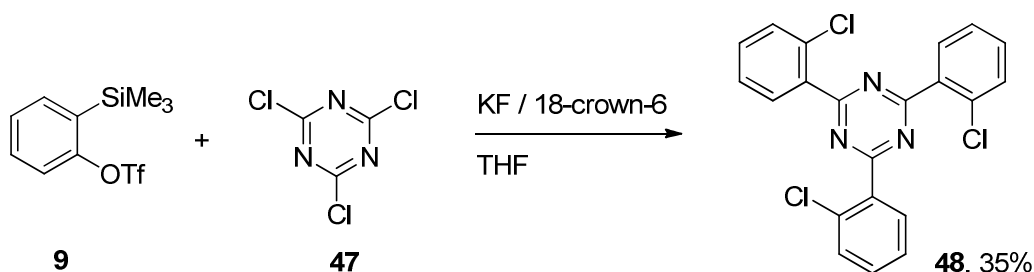
with the presence of sensitive functional groups and the reaction was extended to (*E*)-cinnamoyl chloride **43**, aliphatic acid chlorides, chloroformates and acid bromide **45**, enabling the introduction of acyl and bromo moieties into the adjacent positions of a benzene ring.

This insertion reaction which provides an acyl group in *ortho*-position of an aromatic halide has high synthetic utility since classical methods of acylation of aromatic rings such as Friedel-Crafts acylation reactions of aromatic halides afford mainly or solely *para*-substituted products.⁵⁹



Scheme 1.15. Insertion of arynes into carbon-halogen σ -bonds.

Two years later, Yoshida's group reported the more exotic insertion reaction of arynes into carbon-chloride σ -bond of chlorotriazines, leading to the formation of triarylated triazines.⁶⁰ However, this reaction proved to be only applicable for electronically activated chlorotriazine substrates such as dichlorotriazines and cyanuric chloride **47**, monochlorotriazine being not reactive enough. Nevertheless, the transformation appeared to be a novel approach for constructing aryl–heteroaryl bonds, albeit in low to modest yields (Scheme 1.16).

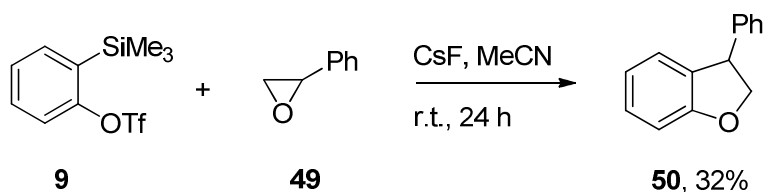


Scheme 1.16. Insertion of benzyne into cyanuric chloride **47**.

1.1.2.3 Carbon-oxygen σ -bond

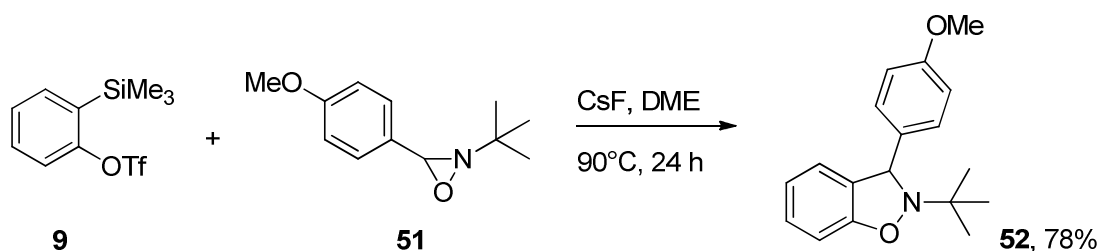
Highly strained three-membered heterocycles such as epoxides and oxaziridines, containing a weak carbon-oxygen bond, have shown to exhibit high reactivity with benzyne. These two classes of substrates were very valuable precursors as they enabled quick access to heterocycles of particular interest in medicinal chemistry.

Dihydrobenzofuran **50** was synthesised by the insertion of benzyne into the carbon-oxygen σ -bond of styrene oxide **49** (Scheme 1.17).⁶¹ The ring expansion proceeded by nucleophilic attack of the oxygen atom on benzyne followed by intramolecular cyclisation at the most reactive benzylic position and terminated by the epoxide ring opening.



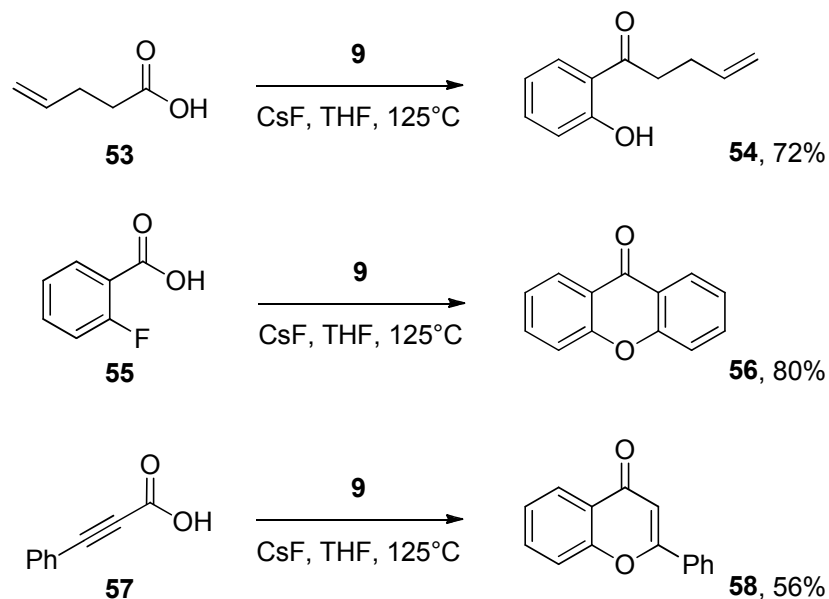
Scheme 1.17. Synthesis of dihydrobenzofuran by insertion of benzyne into the C-O σ -bond of epoxide.

On the other hand, Larock and Kivrak have worked on the synthesis of substituted dihydrobenzisoxazoles by reaction of oxaziridines with arynes.⁶² The reaction occurred smoothly in the presence of excess CsF in DME at 90 °C and a wide range of functional groups were tolerated (Scheme 1.18). Based on previous work by Danishefsky *et al.* on the [3+2] cycloaddition reaction of nitrones with arynes,⁶³ Larock and Kivrak suggested that the mechanism involved in the transformation of oxaziridines would be more likely to happen *via* a [3+2] cycloaddition mechanism rather than a carbon-oxygen σ -bond insertion reaction. However, the authors proposed both mechanisms and did not reject the insertion pathway.



Scheme 1.18. Formation of dihydrobenzisoaxazoles by ring expansion reaction of oxaziridines with benzyne.

A novel route to biologically and pharmaceutically important *ortho*-hydroxyaryl ketones **54**, xanthenes **56**, 4-chromanones, and flavones **58** has also been developed by Larock and Dubrovskiy in 2010. The reaction proceeded by addition of the carbon-oxygen σ -bond of carboxylic acid to arynes.⁶⁴ CsF and THF at high temperature (125 °C) were required for the reaction to take place and to avoid the facile formation of simple phenyl esters by *O*-arylation (Scheme 1.19).⁶⁵

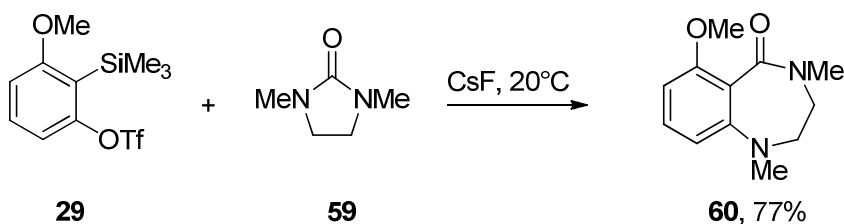


Scheme 1.19. Insertion of benzyne into the carbon-oxygen σ -bond of carboxylic acids.

1.1.2.4 Carbon-nitrogen σ -bond

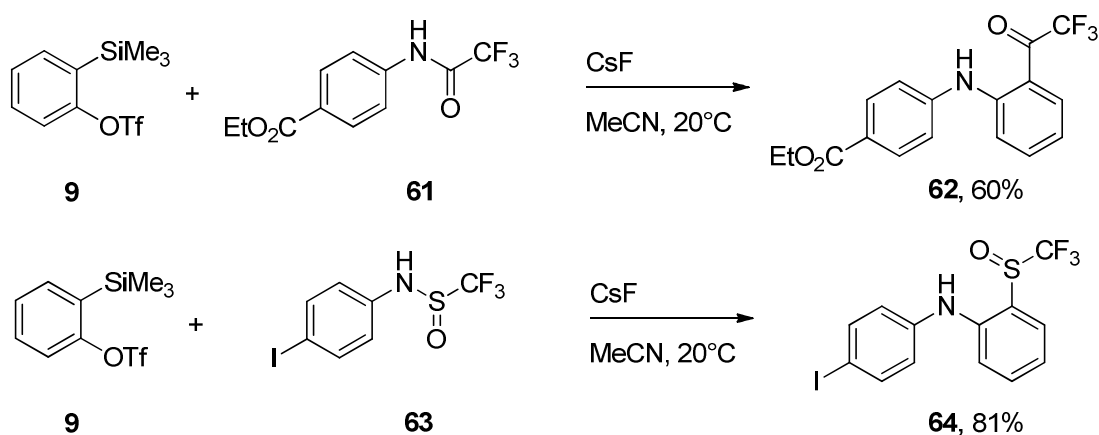
Surprisingly, knowing the nucleophilic character of the nitrogen atom only two reports of carbon-nitrogen σ -bond addition to arynes exist.

Yoshida and co-workers described the addition N-CO σ -bond of ureas to arynes, leading to the one-step synthesis of a wide variety of biologically active 1,4-benzodiazepines and 1,5-benzodiazocines.⁶⁶ Reactions were carried out under mild conditions (CsF, 20 °C) and the insertion was selective for the urea moiety creating cyclic and acyclic 2-aminobenzamide derivatives perfectly unreactive under these reaction conditions (Scheme 1.20). The authors suggested that the mechanism of the reaction occurred *via* nucleophilic additions of a urea nitrogen atom to the aryne giving a zwitterionic species, which evolved to the product by intramolecular nucleophilic substitution at the carbonyl carbon atom.



Scheme 1.20. Insertion of arynes into N-CO bond of ureas, synthesis of 1,4-benzodiazepines.

The second and last example of N-C σ -bond insertion was reported by Larock and Liu.⁶⁷ Although amide compounds synthesised in the previous example were unreactive towards aryne insertion reaction, *N*-phenyltrifluoroacetamide **61** having a highly activated amide bond underwent rapid addition to the triple bond of arynes under mild conditions (Scheme 1.21). The chemistry developed was selective for trifluoroacetamides and other analogue substrates such as trichloroacetamides and unactivated amides failed to provide any product. However, the methodology has also been applied to activated trifluoromethanesulfinamide derivatives **63** and good to excellent yields were also achieved.



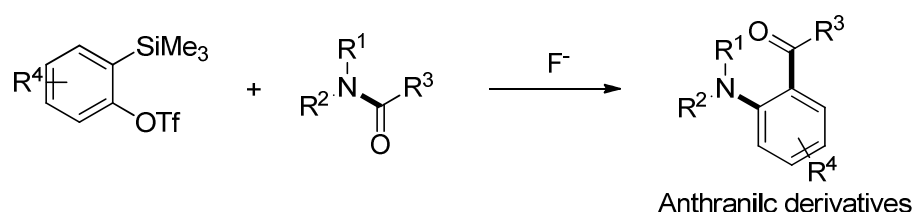
Scheme 1.21. Addition of activated trifluoroacetamides and sulfinamides to benzyne.

As we have seen, significant amounts of research into the insertion of aryne into element-element σ -bond have been reported. However, large disparity between the classes of σ -bond targeted exists and novel insertion reactions have yet to be discovered.

1.1.3 Emerging idea

Carbon-carbon bond cleavage reactions have been particularly studied as they allow the smooth and facile creation of new C-C bonds within one step. On the other hand, the addition of carbon-nitrogen σ -bond to aryne which has great potential for the preparation of highly valuable molecules and building blocks is limited to two restricted examples.

The two methodologies described just above allow the insertion of benzyne into a nitrogen-carbonyl σ -bond (N-CO) of ureas and activated amides, leading to the formation of anthranilic derivatives which contain an amino group and a carbonyl moiety in *ortho*-relationship (Scheme 1.22).⁶⁶⁻⁶⁸



Scheme 1.22. General synthesis of anthranilic derivatives *via* N-CO arynes insertion.

The anthranilic scaffold has important applications in the pigment and dye industry^{69,70} but it is also used in medicinal chemistry for many years.⁷¹ Indeed, anthranilic derivatives constitute an essential motif in the heterocyclic framework of benzoxazines (**65**, Etifoxine),⁷² oxcarbazepines (**66**, Trileptal),⁷³ and benzodiazepines (**67**, diazepam)^{74,75} which are commercially used as anxiolytic and anticonvulsant drugs (Figure 1.3).

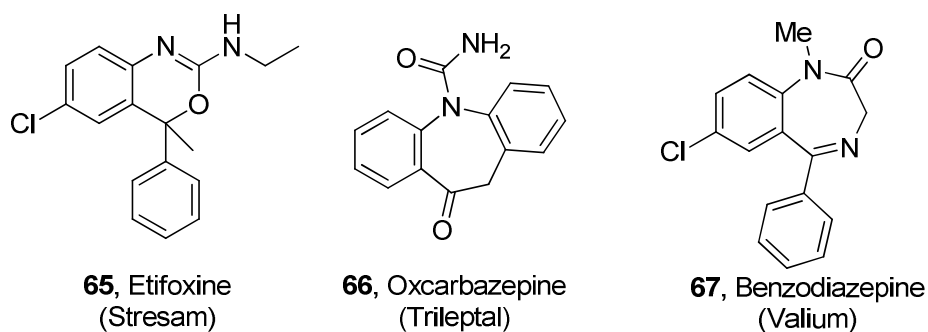


Figure 1.3. Example of anxiolytic and anticonvulsant drugs.

They have also been used for the preparation of quinazolinone, quinoline, and acridone alkaloids.^{76,77} These heterocyclic scaffolds are privileged structures in medicinal chemistry, and anticancer agents such as Raltitrexed **68** (Tomudex, marketed for colorectal cancer), Ispinesib **69** (phase II for solid tumors), and Tempostatin **70** (phase II for bladder cancer) are on the market or in clinical trials. (Figure 1.4).

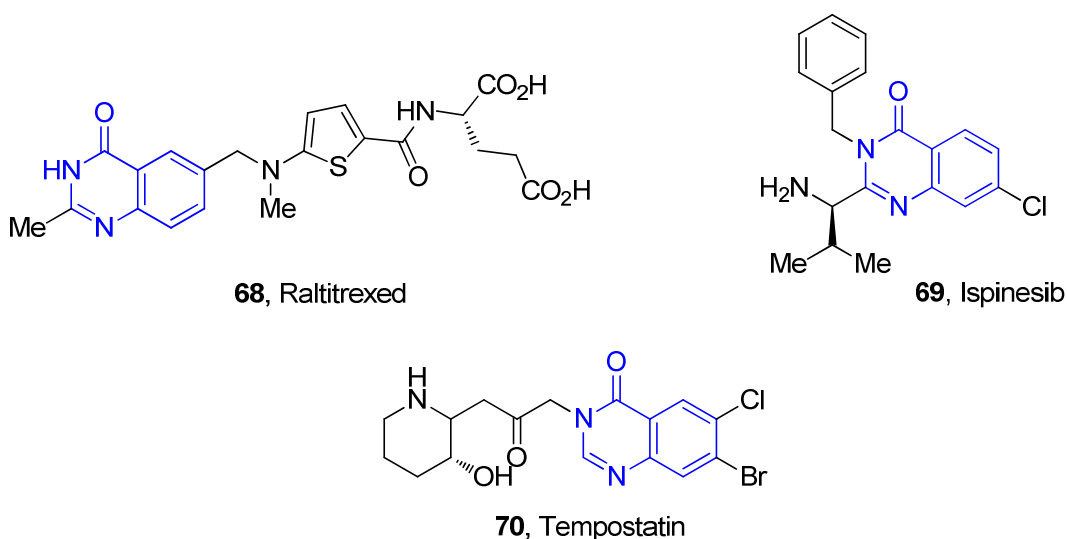


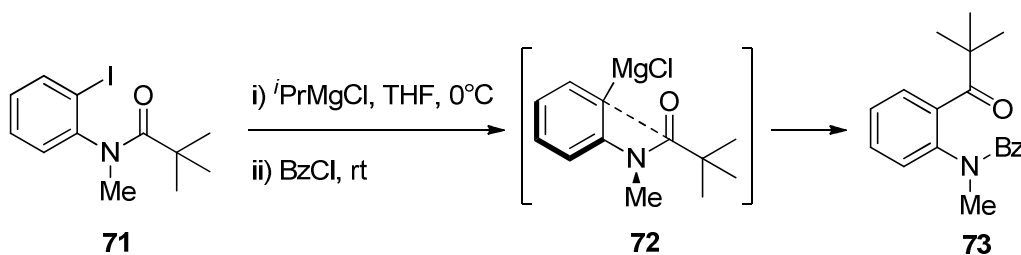
Figure 1.4. Quinazolinone drugs presenting anticancer properties.

Despite the importance given to this scaffold, synthetic routes for the preparation of substituted anthranilic derivatives are limited and involve quite often harsh reaction conditions or the use of transition-metals.

The *ortho*-directed metalation technique is one the most classical method for the preparation such frameworks. Thus, anthranilic derivatives can be obtained by *ortho*-lithiation of anilines by strong lithiated bases and coupling with carboxylic esters.⁷⁸

Based on the same *ortho*-lithiation principle, the *N*-Fries rearrangement reaction of amides or ureas is also a popular method for making these anthranilic substrates.⁷⁹⁻⁸¹

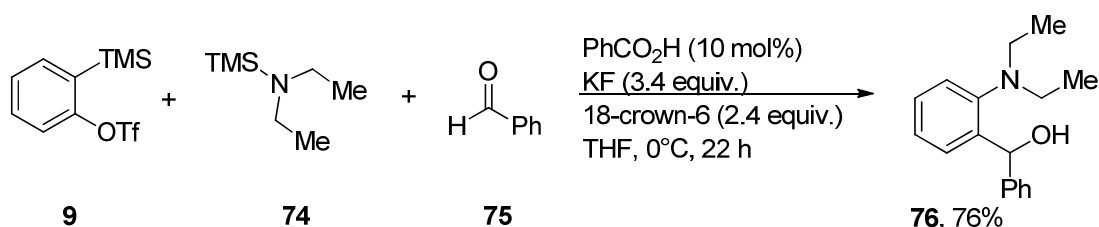
However, this rearrangement is also promoted by strong bases such as *t*-BuLi or Grignard reagents and compounds bearing sensitive functional groups cannot be used with this chemistry (Scheme 1.23).



Scheme 1.23. *N*-fries rearrangement, synthesis of anthranilic derivative.

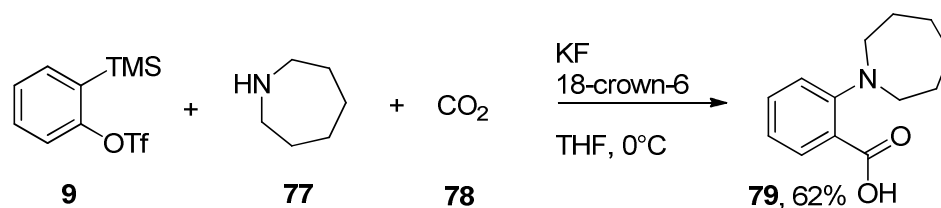
Transition-metal catalysed reactions involving Ullmann type arylation reaction,⁸² palladium catalysed C-H carboxylation⁸³ or C-H carbonylation⁸⁴ reactions have also proved to be successful synthetic routes. Despite the fact that these procedures are catalytic, the scale up of such reactions would require unacceptable amount of catalyst.

A few benzyne reactions have also been reported for the synthesis of anthranilic derivatives. Three-component coupling reactions (TCC) using arynes, aminosilanes and aldehydes permitted the incorporation of amino and hydroxymethyl groups into 1,2-positions of aromatic rings (Scheme 1.24).^{85,86}



Scheme 1.24. Three-component coupling arynes, aminosilanes and aldehydes.

Yoshida *et al.* also described the three-component coupling of arynes, secondary amines and carbon dioxide as a rapid entry for anthranilic acids (Scheme 1.25).⁸⁷ The authors suggested that the zwitterionic aniline species created after the attack of the amine **77** on benzyne **9**, could coordinate to CO₂ **78**, trapping it to provide anthranilic acid through proton migration.



Scheme 1.25. Three-component coupling of arynes, amines and carbon dioxide.

Since, the insertion reaction of benzyne into the nitrogen-carbonyl σ -bond has not been well investigated and that the 1,2-amino-ketoarenes issues of this reaction are highly valuable, we decided to develop a novel and general synthetic route to anthranilic substrates using benzyne (Scheme 1.22) and apply the methodology to the synthesis of biologically active targets.

1.2 Results and discussions

1.2.1 Initial screening and optimisation

A set of commercially available or readily prepared amides and carbamate starting materials **80** to **84** was used to test the reaction (Figure 1.5). Functional groups on both sides of the amide carbonate bond were varied in order to cover different classes of substrates. Thus, *N*-aromatic and *N*-alkyl groups were used as well as electronically and sterically different pivaloyl, benzoyl, acetyl and Boc groups were varied at the other end of the N-CO bond.

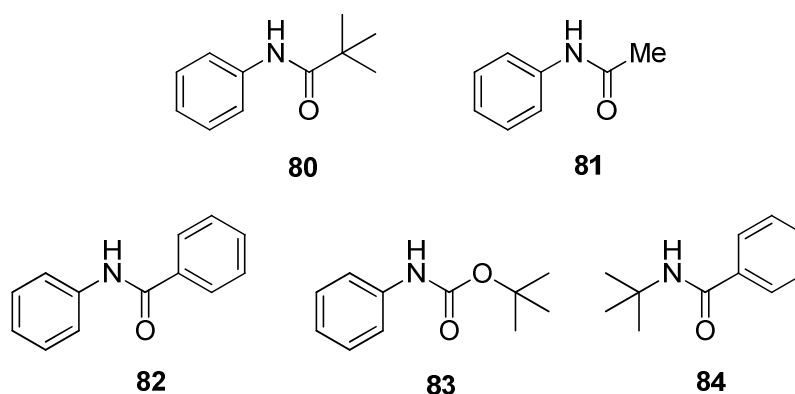
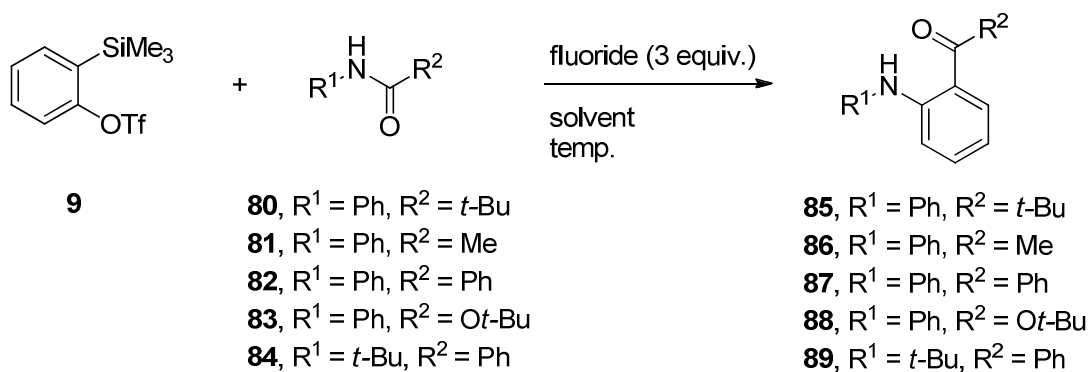


Figure 1.5. Set of substrates used for initial screening.

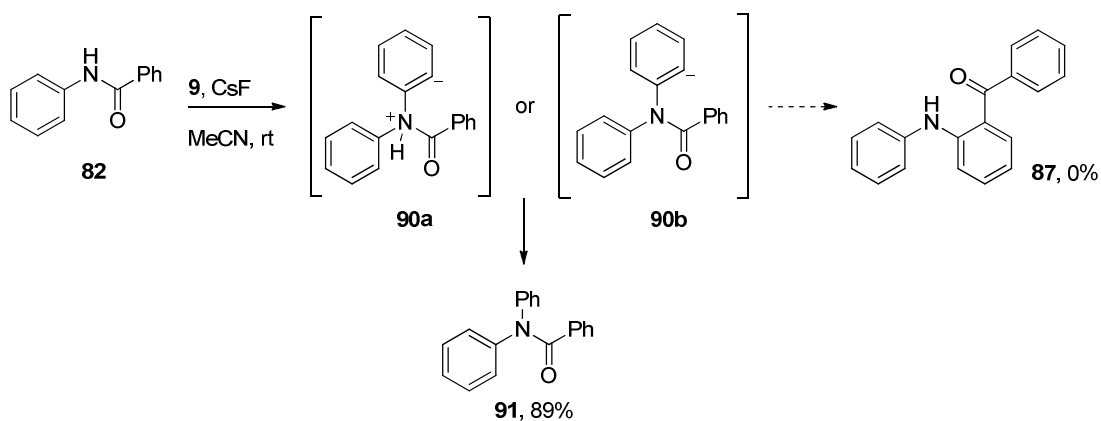
Regular reaction conditions involving stoichiometric amount of CsF (or KF/18-crown-6) and solvents at different temperatures were initially tested (Table 1.1).

Table 1.1. Initial reaction conditions screening



| Entry | S.M. | Fluoride | Solvent | °C | Product (%) |
|-------|------------------------|-----------|-------------------|----------|---------------------|
| 1 | 80 to 84 | CsF | MeCN | rt or 80 | <i>N</i> -arylation |
| 2 | 80 to 84 | CsF | THF | rt or 80 | <i>N</i> -arylation |
| 3 | 80 to 84 | CsF | Tol/MeCN (1:1) | 80 | n.d. |
| 4 | 80 to 84 | CsF | Tol/MeCN (9:1) | 110 | n.d. |
| 5 | 80 to 84 | CsF | DME | rt or 80 | n.d. |
| 6 | 80 to 84 | KF/18-C-6 | MeCN | rt or 80 | <i>N</i> -arylation |
| 7 | 80 to 84 | KF/18-C-6 | THF | rt or 80 | <i>N</i> -arylation |
| 8 | 80 to 84 | KF/18-C-6 | Tol/MeCN (1:1) | 110 | n.d. |
| 9 | 80 to 84 | KF/18-C-6 | DME | rt or 80 | <i>N</i> -arylation |

Initial screening did not show any trace of expected insertion products and under these reaction conditions amides and carbamates presented the same reactivity. Although in most cases starting materials were mainly recovered at the end of the reaction, these compounds were reactive enough to undergo *N*-arylation reactions (Scheme 1.26), as priorly reported by Larock's group.^{32,88}



Scheme 1.26. Pathway for the synthesis of *N*-arylated amides

Thus, this indicated that the nitrogen atom of benzanilide was nucleophilic enough to add onto benzyne. However, it also suggested that either the zwitterionic **90a** or the anionic species **90b** created *in situ* was not able to attack the carbonyl centre and underwent rapid hydrogen abstraction as quenching pathway.

We hypothesised that the proton involved in the protonation step could come from an intramolecular proton transfer from the zwitterion, from the solvent used for the reaction or from the moisture associated with the use of hygroscopic fluoride sources. To rule out the last two hypotheses, we carried out a second set of screening using non-hygroscopic organic soluble fluoride sources and non-protic organic solvent such as toluene.

Table 1.2. Screening of organic soluble fluoride sources.

| Entry | S.M. | Fluoride | Solvent | °C | Product |
|-------|------------------------|----------|-------------------|-----------|--|
| 1 | 80 to 84 | TBAF | MeCN | -20 or rt | SM |
| 2 | 80 to 84 | TBAF | THF | -20 or rt | SM |
| 3 | 80 to 84 | TBAF | Toluene | rt | SM |
| 4 | 80 to 84 | TBAT | MeCN | rt or 80 | <i>N</i> -arylation |
| 5 | 80 to 84 | TBAT | THF | rt or 80 | messy |
| 6 | 80 to 84 | TBAT | DME | rt or 80 | messy |
| 7 | 80 to 84 | TBAT | Tol/MeCN (9:1) | rt or 80 | <i>N</i> -arylation at 80°C 85 = 50 % |
| 8 | 80 to 84 | TBAT | Toluene | 110 | 87 = 55 % 86 = 88 = 89 = 0% |

Reactions involving 1M solution TBAF in THF as the fluoride source failed to provide any expected product. When the reaction was carried out at room temperature, trace amounts of *N*-arylation product could be detected by TLC but starting materials were mainly recovered at the end of the reaction. The temperature of the reaction was decreased to -20 °C in order to slow down the generation of benzyne and to get a better control of the reaction, but this failed to give any product. We then decided to use the tetrabutylammonium triphenylsilyldifluorosilicate salt known as TBAT (Figure 1.6) as fluoride source instead of TBAF.

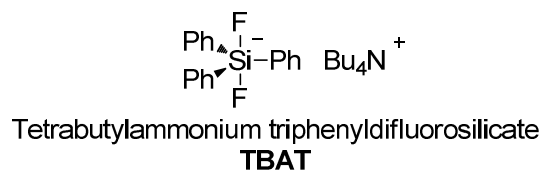
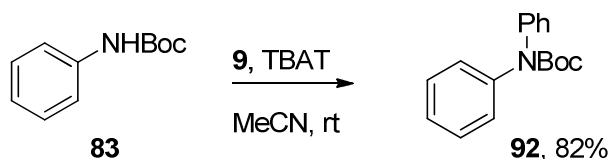


Figure 1.6. Chemical structure of TBAT.

TBAT is a soluble, anhydrous and non-hygroscopic fluoride source that proved to be efficient in some reactions when other fluoride sources such as CsF or TBAF were not.⁸⁹⁻⁹¹

The observed reactivity of TBAT was very different reactivity than TBAF. Indeed, reactions performed in both THF and DME gave complex reaction mixtures with more than eight visible spots on TLC (entries 5 and 6) whereas reactions using TBAF in same solvents gave only starting materials (entry 2).

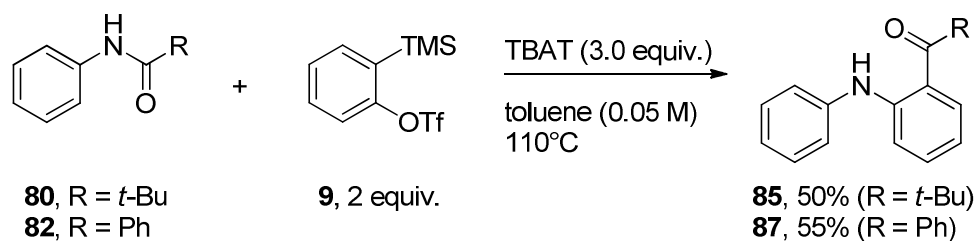
Once again, acetonitrile used in the reaction provided chiefly *N*-arylated products with for example *N*-phenylated product **92** isolated in 82% yield (Scheme 1.27).



Scheme 1.27. *N*-arylation of Boc-aniline using benzyne and TBAT in MeCN.

N-arylation could also be observed when a mixture of toluene/acetonitrile was used. However, due to the low solubility of TBAT in toluene at 20 °C, the temperature of the reaction had to be increased for the *N*-arylation reaction to proceed.

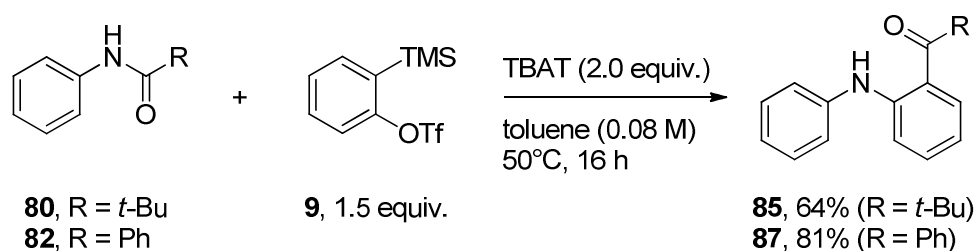
Gratifyingly, when dry toluene was used on its own, insertion products could successfully be synthesised and isolated in promising yields. Indeed, yellow compounds **85** and **87** were isolated in good 50 and 55% yields (Scheme 1.28). However, out of the five starting materials used for the screening only two of them gave the expected products. Other substrates **81**, **83** and **84** gave only the corresponding *N*-arylated species.



Scheme 1.28. Insertion of benzyne into benzanilide and pivaloyl aniline derivative.

Although we could not explain the fact that the reaction seemed to be selective for some substrates, the yields obtained for **85** and **87** were very satisfying and this encouraged us to tune the reaction conditions to get better results. The same set of substrates was used to optimise the reaction conditions and variables such as reaction time, temperature, dilution and stoichiometry were varied.

We were pleased to find out that the fluoride source and benzyne precursor loading could be used in small excess compare to the amides. The temperature of the reaction could also be drastically decreased and a temperature of 50 °C was suitable for the reaction to happen smoothly over 16 hours (Scheme 1.29). Variation of the dilutions did not improve the yields and solvents switches resulted in the complete failure of the reaction. Surprisingly, the reactivity of the five different starting materials explored was identical to that mentioned earlier and only **85** along with **87** could be isolated in good 64 and 81% yields respectively.



Scheme 1.29. Optimised reaction conditions for the insertion of benzyne into the amide bond.

1.2.2 Substrate scope

With our optimised reaction conditions in hands, we decided to investigate the scope of the reaction. A broad set of amides and carbamates were selected to study the substrate range of the reaction. Substrates were directly used as received from chemical suppliers or were synthesised by classic acid chloride coupling to amines.⁹² Moreover, substituents on both sides of the amide bond were varied and functional groups such as alkyl, heterocycles, aromatics and primary, secondary and tertiary amides were tested. The figure 1.7 showed below highlights a selection of compounds tested in the reaction.

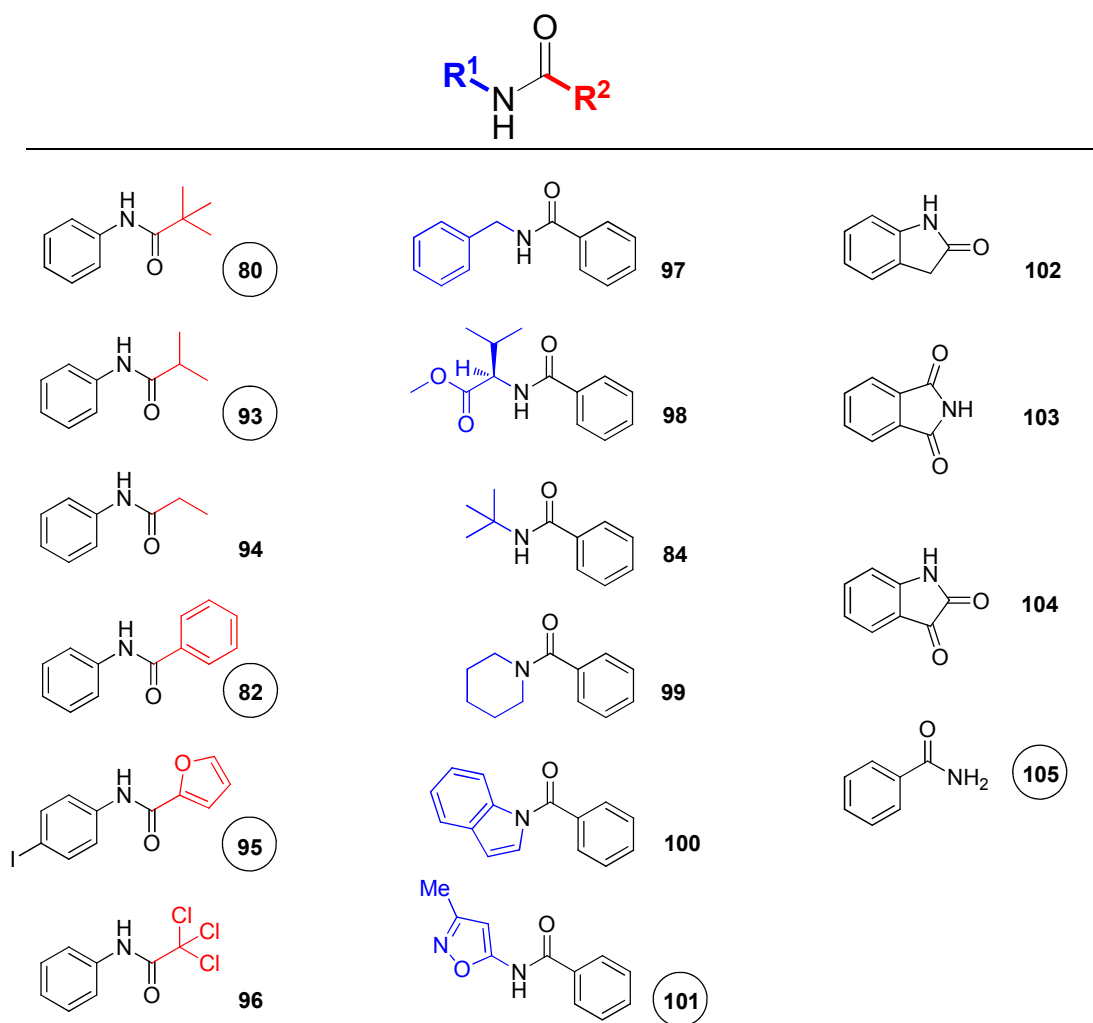
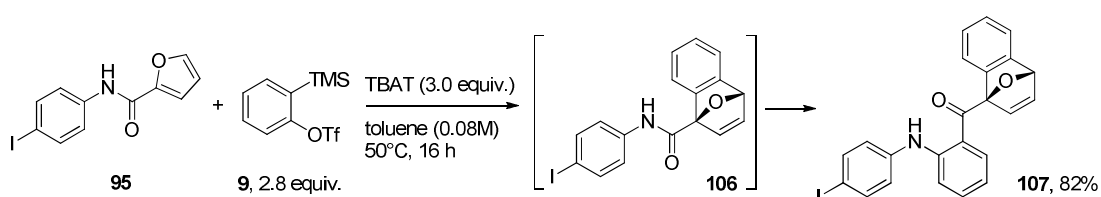


Figure 1.7. Selected set of substrates tested in the reaction.

Circled compound are the compounds that gave the inserted products. We can see from this selection of compounds that amides derived from aniline were more suitable substrates than those issues from alkyl and aromatic amines. This suggests that the electronics on the nitrogen atom of the amide play a large role in the reaction. Indeed, non-aromatic amines such as the amino acid derivative **98** and the benzyl amide **97** failed to give the expected products whereas the aromatic isoxazole derivative **101** gave the product albeit in a modest 30% yield.

Tertiary amides such as **99** and **100** and cyclic amides shown on the right side of the figure 1.7 were not good substrate for the reaction either. Unlike tertiary amides, primary amides such as benzamide **105** reacted with excess benzyne to give benzanilide which reacted further to provide the inserted product. However, the reaction generated unidentified by-products inseparable from the desired product.

Some disparities could also be found when looking at the carbonyl side of the amide bond with aromatic acyl groups being privileged structures for the reaction. Indeed, in the presence of nearly 3 equivalents of benzyne precursor, furan derivative **95** underwent rapid Diels-Alder cycloaddition reaction with benzyne affording the amide intermediate **106** in quantitative yield, which rapidly added to benzyne to generate the inserted product **107** in 82% yield (Scheme 1.30). The structure of the highly functionalised product **107** was secured by X-ray crystallography (Figure 1.8).



Scheme 1.30. Tandem Diels-Alder reaction and benzyne insertion.

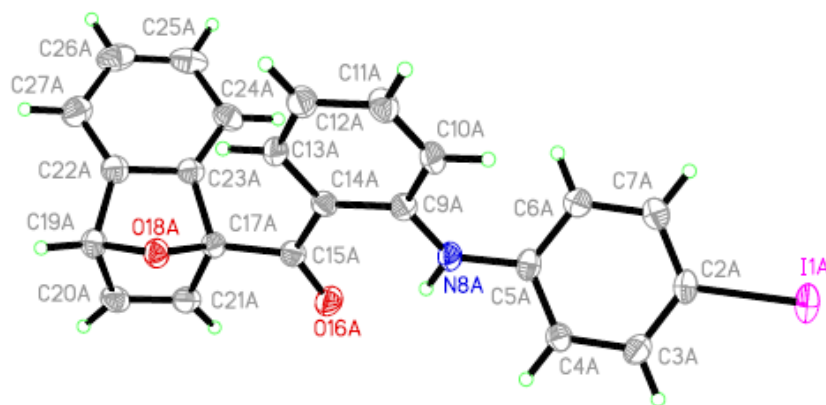


Figure 1.8. X-ray crystallographic data of compound **107**.

Interestingly, large difference in reactivity between alkanoyl substrates could be observed and the reactivity of the insertion reaction decreased when less substituted alkanes groups were employed. Thus, compounds containing a *tert*-butyloyl group reacted better than those having an *iso*-propyloyl group; which reacted better than both unreactive ethyloyl and acetoxy substrates (Figure 1.9). As a matter of fact, compounds containing hydrogens adjacent to the amide bond generally underwent preferable *N*-phenylation under the reaction conditions.

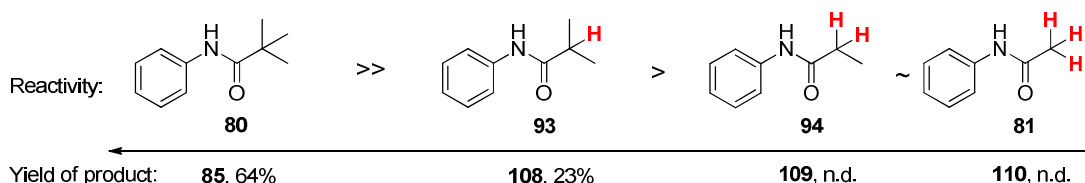


Figure 1.9. Difference in reactivity between alkanoyl amides.

These results indicate that the reaction of insertion is sensitive to substrates containing α -protons on the carbonyl side of the amide bond. This observation is also true for compounds having protons next to the nitrogen atom of the amide.

Given that, we can hypothesise that the nucleophilic attack of the nitrogen occurs in the first place and that the failure to rearrange may be due to an intramolecular proton abstraction in the zwitterion, quenching the reaction.

To gain insight into the quenching pathway involved, we carried out deuterium labelling studies which will be discussed later in the mechanistic section of this chapter.

Having a better understanding of the substrate range suitable for the reaction, we prepared a variety of starting materials to study the reactivity associated with electronic and steric effects. Substituted aryne precursors were also used and the regioselectivity of the reaction controlled. Figure 1.10 below shows the products obtained.

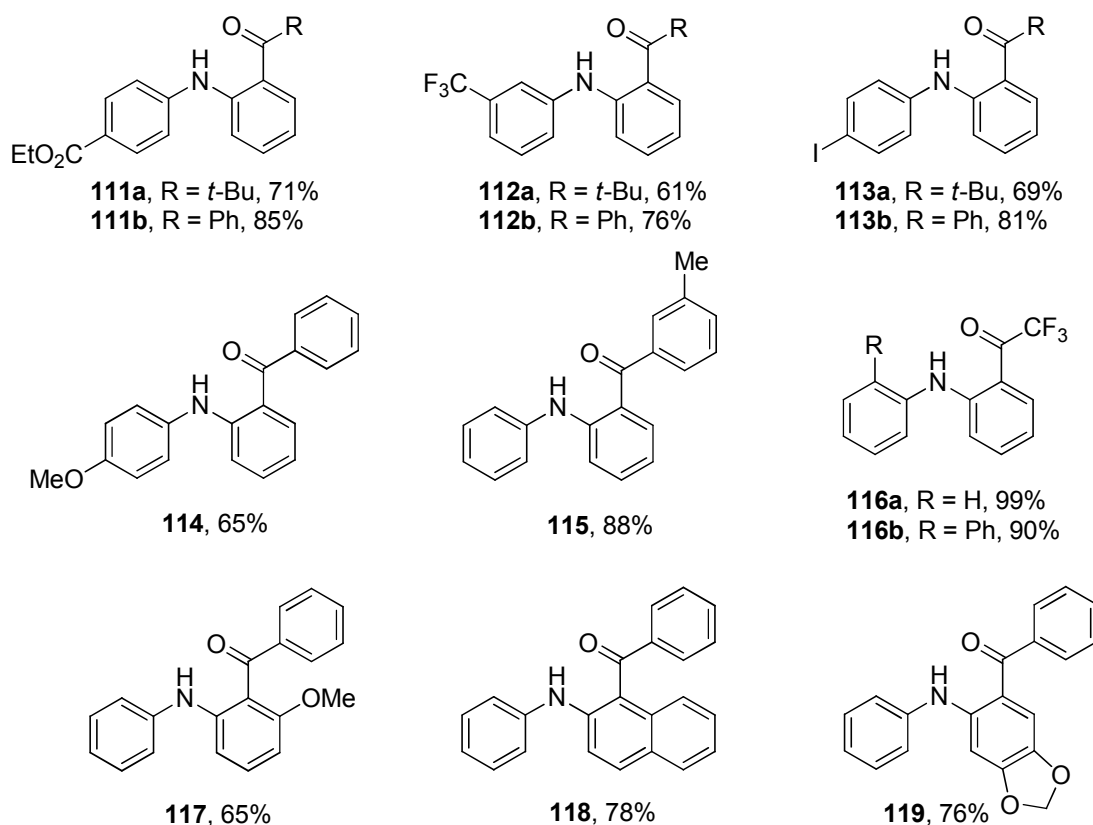


Figure 1.10. Products obtained by insertion of arynes into the σ -bond of amides.

In each case the *N*-*t*-butyl and *N*-phenyl derivatives were similarly efficient substrates. Electron-rich and electron-poor substrates were well tolerated and their reactivity identical. Aromatic halides **113a**, **113b** and **107**, ideal precursors for cross-coupling reactions, were also stable under the conditions and yields up to 80% could be obtained.

Trifluoroacetanilides, previously investigated by Larock *et al.*, were excellent substrates for the reaction.⁶⁷ Indeed, compound **116a** formerly isolated by Larocks' group in 77% yield, could be synthesised in quantitative yield using our reaction conditions. Sterically hindered trifluoroacetanilide derivative **116b**, prepared in very high yield (90%), reflected the high reactivity of trifluoroacetamide starting materials compared to aromatic and alkyl amides.

It should be noted that the reaction of 3-methoxybenzyne and 1,2-naphthalene occurred with perfect regioselectivity. In the case of unsymmetrical arynes, the observed regioselectivity was ascribable to steric and/or electronic effects of the substituent on the arynes. For 3-methoxybenzyne and 1,2-naphthalene, the introduction of the nucleophilic moiety happened exclusively at the less sterically hindered position. Moreover, the 3-methoxybenzyne exerted an electron-withdrawing inductive effect, which also directed the nucleophilic attack of the nitrogen towards the *meta*-position compare to the methoxy group (Figure 1.11).³

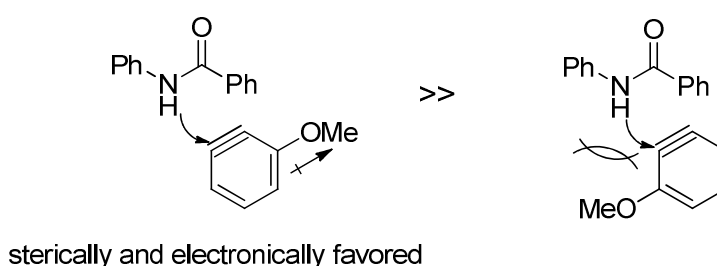
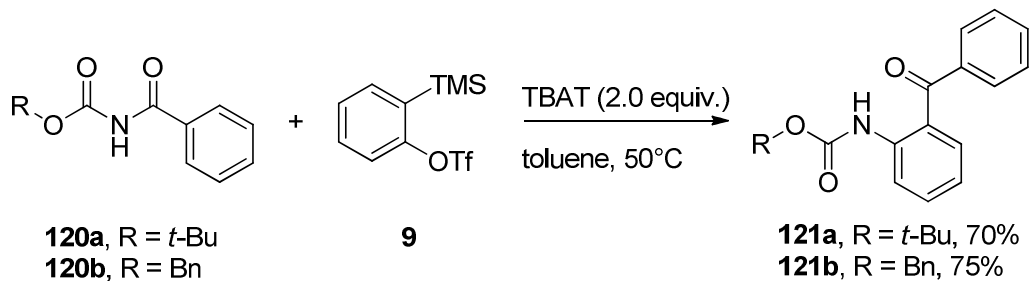


Figure 1.11. Regioselectivity in the reaction of 3-methoxybenzyne.

Eventually, we examined the two protected benzamide derivatives **120a** and **120b** in the reaction, an important substrate class as it permits the preparation of protected amino ketones as versatile building blocks for heterocycle synthesis (Scheme 1.31). Boc-, CBz- and Fmoc-protecting groups were explored. Insertion was selective for

the amide over the carbamate linkage in the case of Boc- and CBz-protecting groups, providing both protected amines **121a** and **121b** in 70% and 75% yield, respectively. Base-labile Fmoc-protecting group was not stable under fluoride conditions and any product was isolated.



Scheme 1.31. Imide insertion.

1.2.3 Conclusion

We successfully managed to develop a new reaction of C-N addition of amides to arynes. The chemistry allows the rapid and smooth insertion of reactive intermediate benzyne into the N-CO σ -bond of aromatic amides using the *O*-triflatophenyl silane benzyne precursors and TBAT in toluene at 50 °C. The methodology developed is high yielding and has been applied to a large set of functionalised amides allowing the synthesis of versatile anthranilic derivatives, ideal precursors for the synthesis of valuable heterocycles.

1.2.4 Acridone and acridine synthesis

1.2.4.1 Biological and chemical properties

The acridone scaffold constitutes the main framework of numerous natural products and synthetic compounds with pharmacological activities.^{76,77,93,94}

For example, acronycine **122** is probably one of the most iconic alkaloid natural products presenting the acridone structure (Figure 1.12). This compound along with other related alkaloids **123** and **124** has shown to exhibit a broad spectrum of activity against numerous solid tumors and has been evaluated in Phase I-II of clinical trials.^{95,96}

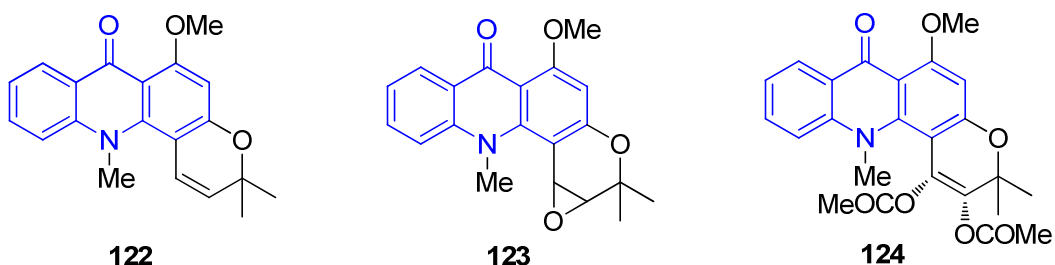


Figure 1.12. Acronycine **122**, Acronycine epoxide **123**, and (±)-*cis*-1,2-Diacetoxy-1,2-dihydroacronycine **124**.

In addition to their anticancer properties, acridones have also demonstrated strong inhibition of HIV-1 replication in chronically infected cells,⁹⁷ and are currently being developed as antimalarial drugs.^{98,99}

On the other hand, acridines, similar substrates to acridones, have also shown important biological activities. Acridines have anticancer properties due to their ability to bind and to intercalate into DNA and to disrupt unwanted cellular processes.¹⁰⁰ Thus for example, acridine compounds such as Amsacrine **125**, used as antineoplastic agent, have shown inhibition activity of the topoisomerase enzyme involved in pancreatic cancer cell proliferation (Figure 1.13).¹⁰¹⁻¹⁰³

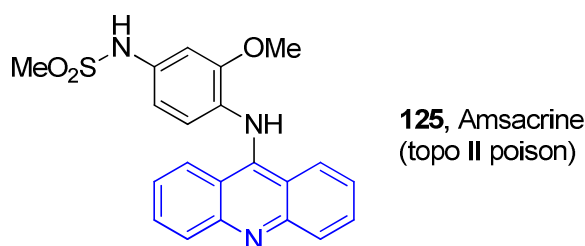


Figure 1.13. Amsacrine **125** an anticancer agent.

This capability to bind to DNA has been exploited in many areas of medicine and significant biological activity towards bacteria,^{104,105} Alzheimer's disease,¹⁰⁶ and HIV replication has also been reported.¹⁰⁷

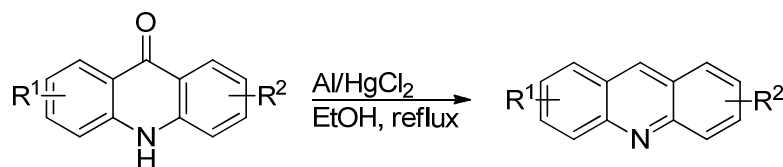
Moreover, due to their highly conjugated π -system, acridines have also been used for their luminescent properties as fluorescent probes in biological targets¹⁰⁸⁻¹¹⁰ and as light emitting materials for application in OLEDs.¹¹¹

1.2.4.2 Acridones, acridines in benzyne chemistry

Most of the synthetic methods used for the preparation of acridones and acridines are empirical and require harsh reaction conditions.

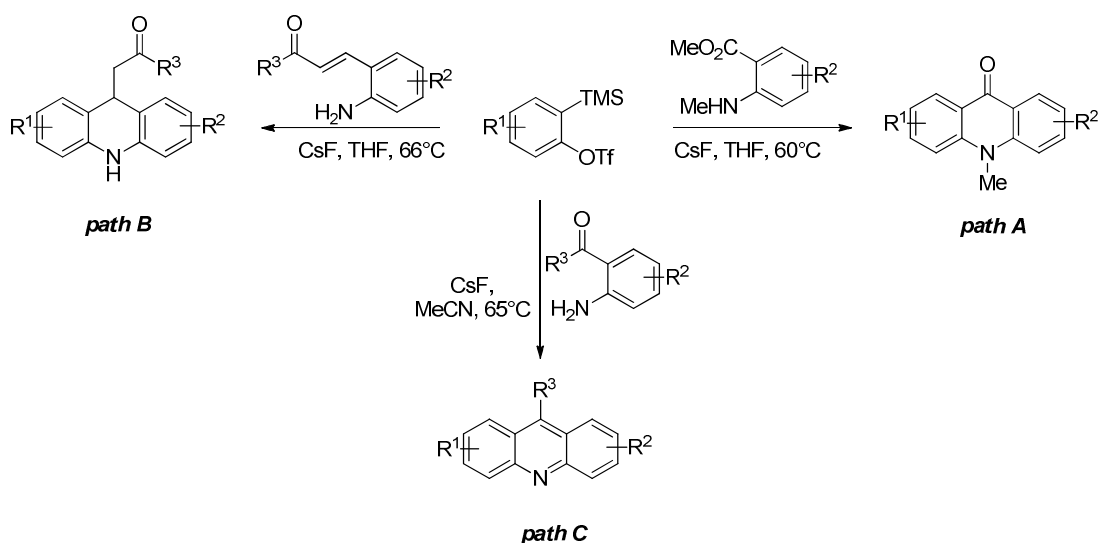
Acridones are usually obtained from Ullmann condensation of anilines with *ortho*-halogen-substituted benzoic acids, generating *N*-phenyl anthranilic acids, which then under high temperatures and strongly acidic conditions undergo intramolecular electrophilic aromatic substitution.¹¹²⁻¹¹⁴

The Bernthsen reaction is probably considered as one of the oldest reactions to make 9-substituted acridine from a diarylamine and a carboxylic acid. This reaction requires stoichiometric amount of zinc chloride and high temperatures to proceed in good yields.^{115,116} Acridines can also be prepared from the reduction of acridones (Scheme 1.32), but as mentioned, acridones are not necessarily easy to prepare.¹¹⁷



Scheme 1.32. Synthesis of acridines by reduction of acridones.

Milder reaction conditions, involving the reactive intermediate benzyne have been developed over the past few years. Specially designed aromatics containing both nucleophilic as well as electrophilic sites have been used to produce acridones and acridines (Scheme 1.33). Larocks' group used *N*-methyl anthranilic esters to prepare substituted *N*-methylacridones (path A).^{118,119} Similarly, acridines have been obtained by tandem intermolecular nucleophilic coupling and cyclic Michael addition of arynes (path B)¹²⁰ or by [4+2] annulation of arynes and 2-aminoaryl ketones (path C).¹²¹

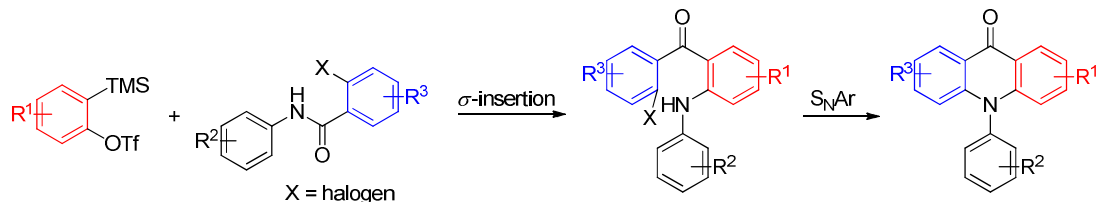


Scheme 1.33. Syntheses of acridones and acridines using arynes.

Considering the fact that anthranilic derivatives have been successfully used in benzyne chemistry for the synthesis of such heterocycle, we decided to extend our methodology to the novel synthesis of acridones and acridines.

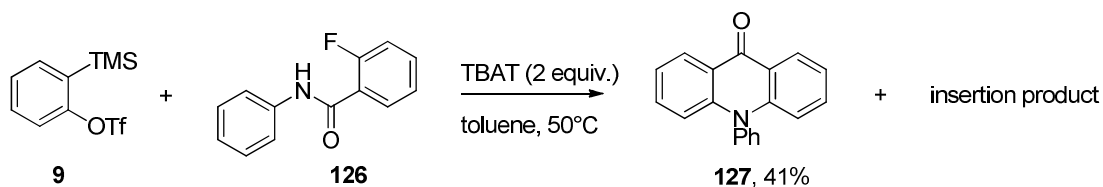
1.2.4.3 Acridones synthesis

We thought to access acridones from readily available *ortho*-halobenzamides as starting materials through initial aryne σ -insertion, followed by an in situ intramolecular S_NAr reaction (Scheme 1.34).



Scheme 1.34. Synthesis of acridones: cascade benzyne insertion- S_NAr reaction.

The reaction of *ortho* fluorobenzamide **126** with benzyne precursor **9** under the conditions developed for the insertion reaction gave very promising results. Indeed, *N*-phenyl acridone **127** could be isolated in 41% yield along with some non-cyclised insertion product when the reaction was carried out overnight at 50 °C (Scheme 1.35). Thus, this encouraged us to find the best reaction conditions in order to develop a new one-pot procedure for the synthesis of acridones from simple arylamides.



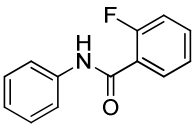
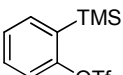
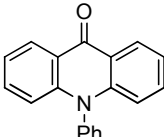
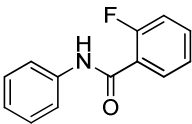
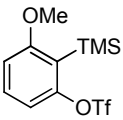
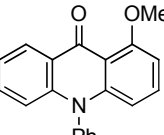
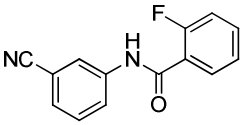
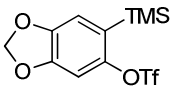
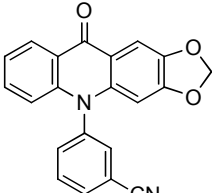
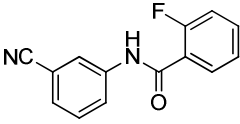
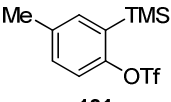
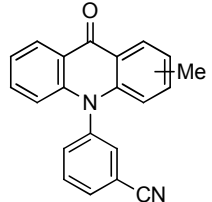
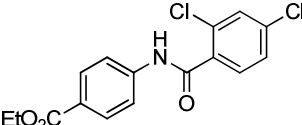
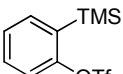
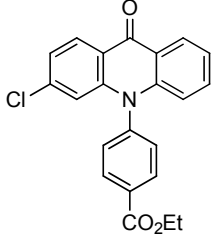
Scheme 1.35. One-pot synthesis of *N*-phenyl acridone **127** from arylamide.

The same reaction performed at 65 °C for 5 hours and heated up to 120 °C for 2 hours gave the product in 67% yield and indicated that the reaction had to be carried out at higher temperature for the intramolecular nucleophilic aromatic substitution to happen efficiently.

Knowing that versatile *O*-triflatephenyl silane benzyne precursors can be used at high temperature in microwave-assisted conditions,^{122,123} we decided to investigate the reaction under irradiation conditions.

Very rapidly we found out that only five minutes of microwave irradiation at 120 °C in the presence of TBAT were required to obtain excellent yields (Table 1.3)

Table 1.3. Acridone synthesis.

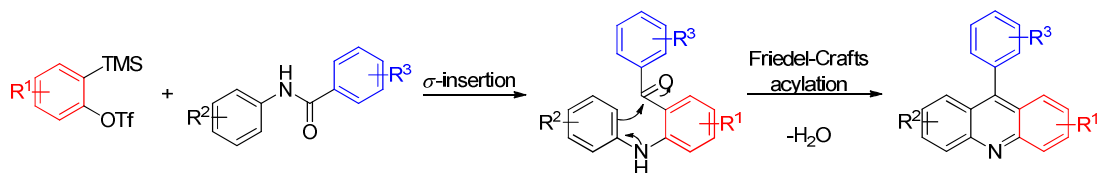
| entry | SM | BP | Product | Yield (%) |
|-------|---|---|--|-------------|
| 1 |  126 |  9 |  127 | 92 |
| 2 |  126 |  29 |  128 | 62 |
| 3 |  129 |  15 |  130 | 89 |
| 4 |  129 |  131 |  132a + 132b | 85 (1:1) |
| 5 |  133 |  9 |  134 | 88 |

Functional groups on both amide and benzyne precursors were well tolerated and yields of acridones were generally good to excellent. 3-Methoxybenzyne afforded a single regioisomer (table 1.3, entry 2), whereas a 1:1 separable mixture of regioisomeric acridones was obtained when the 3-methylbenzyne precursor **131** was used (entry 4), underlining the intermediacy of the reactive aryne intermediate in the reaction. Different halide leaving groups were screened and best results were

obtained for fluorine and chlorine atoms. Less readily available *ortho*-bromo- and *ortho*-iodo-compounds lead to the formation of multiple by-products.

1.2.4.4 Acridine synthesis

Following the success of the development of the single-step method for the synthesis of acridones, we were encouraged to develop another one-pot procedure for the preparation of acridines from *N*-phenyl anthranilic derivatives. We thought that an acid-mediated intramolecular Friedel-Crafts acylation reaction followed by dehydration would be a suitable route to substituted acridines (Scheme 1.36).



Scheme 1.36. Acridines synthesis *via* benzyne insertion and Friedel-Crafts acylation.

Our approach was to achieve the first insertion step as usual and then to carry out the second step by adding a Lewis acid to the crude mixture. Therefore, a small variety of commonly used Lewis acids were screened: AlCl_3 , FeCl_3 , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, TiCl_4 , SnCl_4 and $\text{BF}_3 \cdot \text{OEt}_2$. We were very pleased to see that all Lewis acid tested gave the desired product after heating up the solution for 16 hrs at 80 °C. Aluminium and iron trichloride promoted efficiently the formation of acridines with complete disappearance of the starting material. However workups associated with these reactions were very messy and difficult to do, resulting in modest isolated yield of acridines. On the other hand, reaction involving titanium and tin tetrachloride were easy to workup but they did not provide full consumption of the starting material after overnight reaction. Eventually, boron trifluoride etherate stood out from the other Lewis acids, affording clean reaction mixtures and showing great efficiency (Figure 1.14).

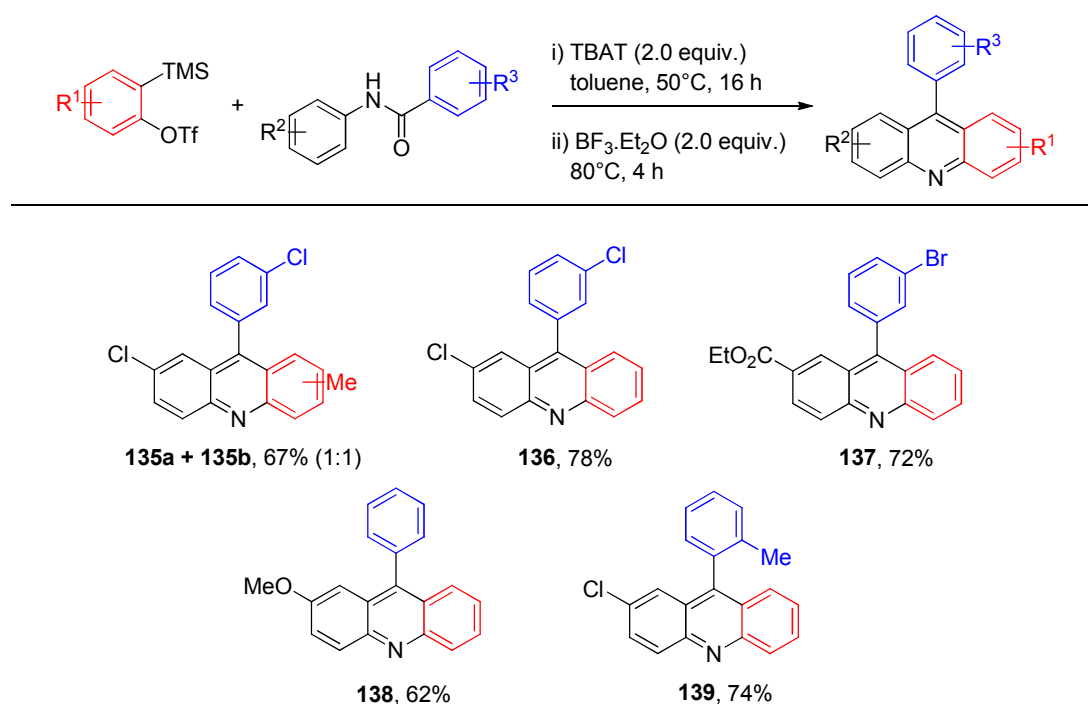


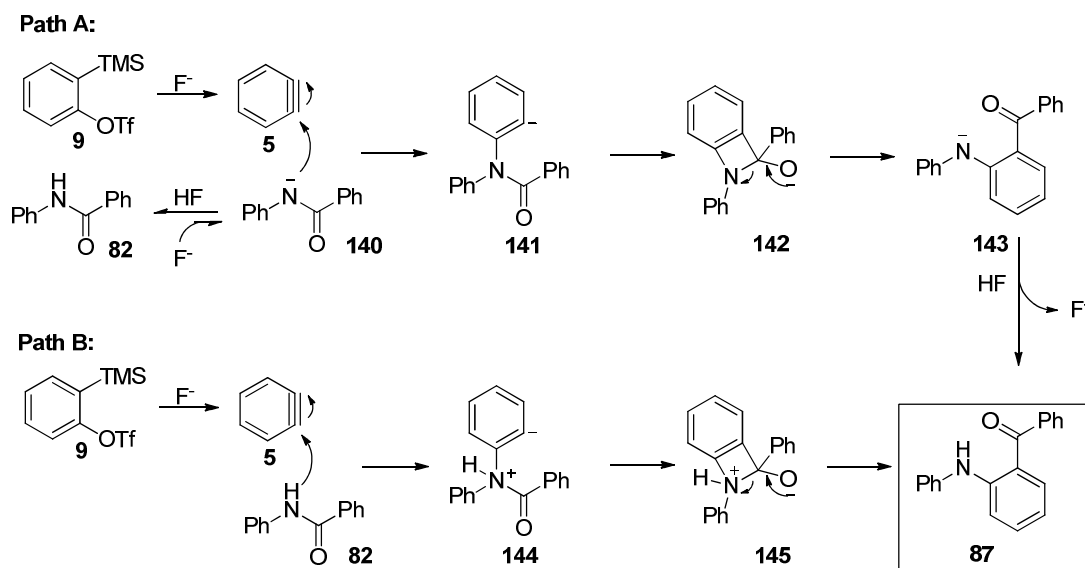
Figure 1.14. Acridine synthesis.

Similarly to the acridones synthesis, we successfully developed a one-pot procedure for the synthesis of highly substituted acridine derivatives. Substrates bearing electron-donating and –withdrawing groups were equally efficient and sensitive functional groups such as the carboxylic ester were well tolerated under these mild reaction conditions.

Each synthesis incorporates the aryne moiety into the heterocycle framework and can be directed towards the display of either *N*-aryl (acridones) or *C*-aryl (acridines) groups according to the cyclisation conditions.

1.2.5 Mechanistic studies

Deuterium labelling experiments have been carried out to get some insight into the mechanism of the reaction. As previously suggested by Larock and co-workers,⁶⁷ the reaction of insertion of benzyne into N-CO σ -bond could occur *via* two different pathways (Scheme 1.37).

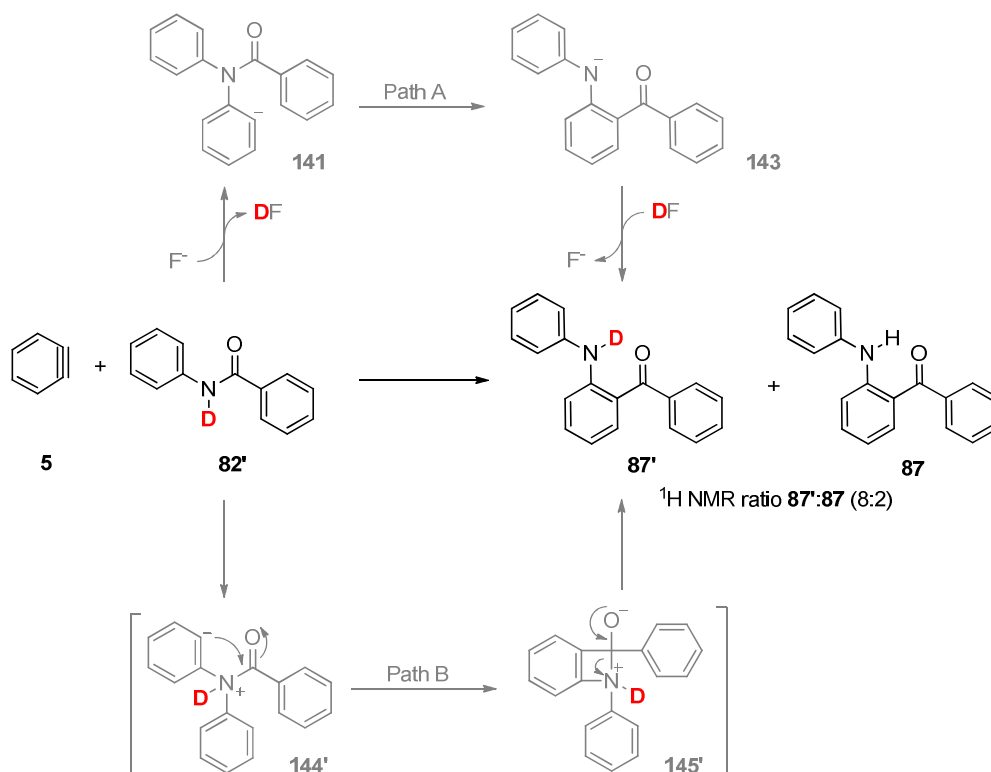


Scheme 1.37. Possible mechanisms involved during the insertion reaction.

In path A, the fluoride source can both react with the benzyne precursor and act as a base strong enough to abstract the proton on the nitrogen atom of the amide to afford anion **140**, which can undergo nucleophilic addition on benzyne to produce the anionic intermediate **141**. Then, this intermediate **141** can rapidly attack in an intramolecular fashion the carbonyl carbon to generate the unstable cyclobutane intermediate **142**, which readily ring opens and gets protonated to give the final C-N insertion product.

The mechanism involved in path B is very similar to the mechanism described in A. The main difference is that the fluoride source is not basic enough to deprotonate the amide therefore zwitterionic species **144** and **145** are implicated in the process.

To determine which mechanism was involved in our chemistry, benzanilide **82'** deuterated on the nitrogen atom was prepared and the stability of the deuterium atom in the reaction was monitored by ^1H NMR (Scheme 1.38).



Scheme 1.38. Mechanistic studies.

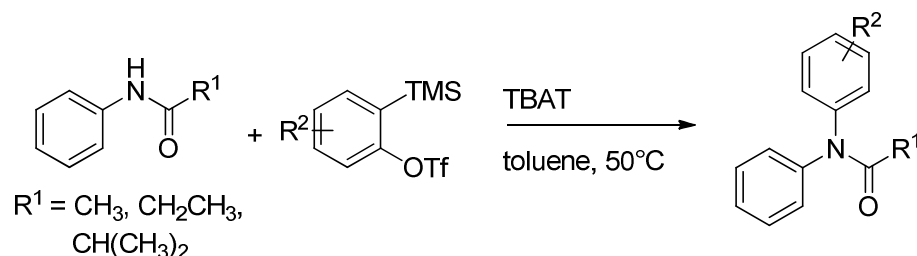
After evaporation of the toluene and ^1H NMR of the crude mixture, we clearly identified that 80% of the product formed in the reaction still contained the deuterium atom previously introduced.

Path B shown in scheme 1.38, involving the formation of zwitterionic species could be considered as a reasonable route to the product. Indeed, in path B, the amide **82'** is not deprotonated and that the deuterium atom on the nitrogen atom is carried all the way through to the product **87'**, which is in accordance with the results obtained.

On the other hand, path A could also be seen as a possible pathway to the final product **87'**. Indeed, the fluoride anion in solution could act as a deuterium (or proton) shuttle between the starting material **82'** and the observed product **87'** by deprotonation of the amide **82'** and protonation of the anionic species **143** at the end of the reaction (Scheme 1.38, path A).

As both pathways are conceivable, it is not possible to conclude on the precise mechanism of the reaction.

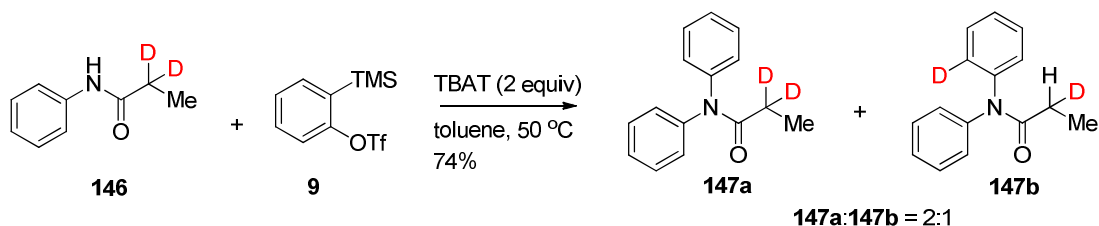
We then decided to get a better understanding of the fact that compounds having hydrogen atoms adjacent to the amide bond provided exclusively *N*-phenylated products and failed to give the expected insertion products (Scheme 1.39).



Scheme 1.39. Substrates limitation of the insertion reaction.

To make sure that the failure of insertion was related to the type of substrates used and not to a fast proton abstraction by the zwitterion from elsewhere (solvent or TBAT), we carried out the reaction in dry deuterated benzene (C_6D_6). ^1H and ^2H NMR of the product obtained after reaction in deuterated solvent did not reveal any incorporation of deuterium atoms on the molecule. Thus, this suggested that the protonation of the intermediate was not related to the solvent but directly to the substrate or the fluoride source.

Therefore, doubly deuterated *N*-phenylpropionamide **146** was prepared to study if an intramolecular abstraction of the α -proton by the zwitterion was responsible in the failure of the reaction (Scheme 1.40).



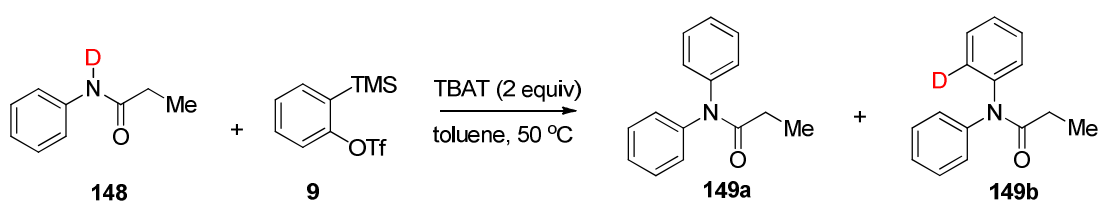
Scheme 1.40. First intramolecular quenching pathway.

After purification of the reaction mixture, we carried out on a sophisticated NMR spectrometer (800 MHz) some ^1H , ^2H and ^{13}C NMR analyses in order to detect even traces amounts of protonation and/or deuterium shift on the product mixture.

Although the ^1H NMR analysis of the starting material did not reveal any signal around 2-2.5 ppm, the ^1H NMR of the product mixture showed a signal in this region characteristic of hydrogens incorporation and deuteriums substitution on the propionoyl moiety. Moreover, terminal methyl signal formerly appearing as a singlet in the starting material appeared as a small doublet in the product.

Once again the incorporation of hydrogen atoms next to the carbonyl group was secured by ^{13}C NMR analysis which showed distinctively two different NMR signals ($-\text{CD}_2-$ and $-\text{CHD}-$). While, it was difficult to identify by ^1H and ^{13}C NMR if deuterium atoms were incorporated into the aromatic moiety, ^2H NMR clearly showed the presence of deuteriums on the phenyl ring. NMR quantification indicated a ratio 2:1 of **147a** and **147b** which demonstrated the intramolecular 1,5-hydrogen abstraction pathway as a quenching mechanism for alkyl-substituted amide substrates.

Another quenching pathway could also be identified when alkyl amides were used. This pathway was likely to happen from transfer of the amide proton to the aromatic anion. This intramolecular transfer has been confirmed by reacting the *N*-deuterated derivative **148** with benzyne and observing deuterium incorporation into the aryl ring of the product by ^2H NMR analysis (Scheme 1.41).



Scheme 1.41. Second intramolecular quenching pathway.

However, it is not perfectly clear yet why alkyl amides underwent this quenching pathway whereas aromatic amides did not. We thought that carbonyl groups of alkyl amides were less activated than aromatic amides; therefore alkyl zwitterionic species were more likely to be quenched by a rapid intramolecular hydrogen shift before they had time to attack the carbonyl centre.

1.3 Conclusion

The insertion of arynes into the nitrogen-carbonyl σ -bond has been studied and we successfully developed a general method for the addition of amide derivatives to benzyne. The chemistry applicable to *N*-aromatic amides occurs under mild reaction conditions and is used to prepare in good to excellent yields, highly substituted anthranilic derivatives which are critical building blocks for heterocycles synthesis. The methodology set up has been expanded to the rapid and smooth synthesis of biologically active heteroaromatics. A single-step sequence of arynes σ -bond insertion followed by intramolecular S_NAr cyclisation permitted access very quickly and in high yields to substituted acridone derivatives. Acridines were also synthesised by developing a very efficient one-pot procedure: arynes σ -bond insertion and Friedel-Crafts acylation reaction.

The mechanism of the reaction has also been studied in detail by performing several deuterium labelling experiments and has demonstrated the involvement of a key zwitterionic species in the mechanism.

This chemistry has inspired other related projects in the group and insertion reactions of arynes into the σ -bond of thioesters¹²⁴ or the π -bond of thioureas¹²⁵ are underway.

1.4 Experimental

1.4.1 General methods

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brüker dpx360 (360 MHz) instrument and calibrated to residual solvent peaks: proton (CDCl_3 7.26 ppm) and carbon (CDCl_3 77.0 ppm). ^2H NMR spectra were recorded on a Brüker ava800 (800 MHz) instrument. The ^1H data is presented as follows: chemical shift (in ppm on the δ scale), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), the coupling constant (J, in Hertz) and integration. The ^{13}C data is reported as the ppm on the δ scale followed by the interpretation. Electrospray and electron impact high resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer. The data is recorded as the ionisation method followed by the calculated and measured masses. TLC was performed on Merck 60F254 silica plates and visualised by UV light and/or anisaldehyde or potassium permanganate stains. The compounds were purified by flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. The eluent is quoted as a percentage. Microwave reactions were carried out in a Biotage Initiator using sealed vessels. The temperature of the reaction mixture was monitored using a calibrated infrared temperature control under the reaction vessel. Reactions were performed under nitrogen atmosphere. All solvents were dried before use unless otherwise stated. 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate **9** and tetrabutylammonium difluorotriphenylsilicate (TBAT) were purchased from Sigma-Aldrich Co.

Substituted silylaryl triflates (**15**, **29**, **41** and **131**) and amide starting materials were prepared according to well-known literature procedures and spectroscopic data were in agreement with those formerly published.^{24,27,92} All other chemicals were purchased from chemical suppliers and used as received.

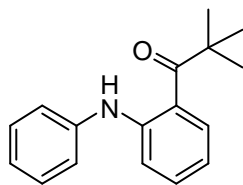
1.4.2 Procedure for the preparation of the starting materials

All of the amides were synthesised using the same procedure.⁹² To a well-stirred solution containing equivalent quantities of the amine (1.1 equiv) and triethylamine (1.1 equiv) in dichloromethane was added a solution of the acid chloride (1.0 equiv) in DCM. The solution was stirred at room temperature for 14 hrs. The resulting solution was extracted twice with saturated solution of NaHCO₃ and washed with brine. The organic layer was dried over MgSO₄ and the solvent removed under vacuum. Crude amide was purified by column chromatography using a mixture of DCM/hexane as the eluent.

1.4.3 Procedure A for amide insertion

All reactions were carried out under the same following reaction procedure, excepted for product **107**. To a microwave vial (2 – 5 mL) was introduced a solution of the amide (0.250 mmol) and TBAT (0.500 mmol) in toluene (3 mL). The vial was then sealed using a serum cap and flushed for approximately 2 min with nitrogen using a balloon of N₂. Liquid aryne precursors (0.375 mmol) were added to the crude mixture using a syringe and the reaction was heated at 50 °C using an aluminum heating block for 16 h. After overnight reaction, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (dry loading) to afford the desired product. The solvent mixtures used for the column chromatography are reported below for each compound.

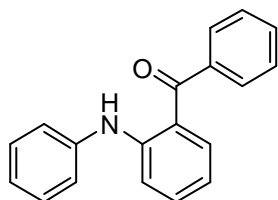
2,2-Dimethyl-1-(2-phenylamino-phenyl)-propan-1-one (85). Prepared according



to the general procedure A using the corresponding amide (45 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (7:3). Isolated as a yellow oil, m = 41 mg. Yield: 64%. R_f [hexane / DCM (6:4)] = 0.62. ¹H NMR (360 MHz, CDCl₃) δ 8.98 (s, 1H), 7.80 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.38 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.32 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.27 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.19 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.04 (dt, *J* = 7.3, 1.2 Hz, 1H), 6.80 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 1.42 (s, 9H); ¹³C NMR (90 MHz, CDCl₃) δ 210.8 (quat), 145.2

(quat), 141.4 (quat), 131.9 (CH), 129.8 (CH), 129.3 (2 CH), 122.7 (quat), 122.5 (CH), 120.8 (2 CH), 117.2 (CH), 116.6 (CH), 44.9 (quat), 28.6 (CH₃): HRMS (ES⁺) cald. for (M+H)⁺ C₁₇H₂₀NO: 254.1539; found 254.1542.

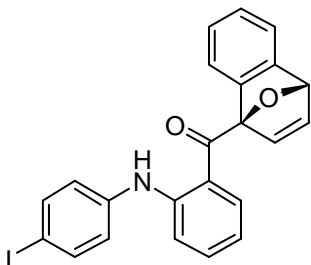
Phenyl-(2-phenylamino-phenyl)-methanone (87). Prepared according to the



general procedure A using the corresponding amide (49 mg), TBAT (270 mg) and **9** (93 μL). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, m = 55 mg.

Yield: 81%. R_f [hexane / DCM (1:1)] = 0.55. ¹H NMR (360 MHz, CDCl₃) δ 10.17 (s, 1H), 7.74 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.59 – 7.54 (m, 2H), 7.52 – 7.49 (m, 2H), 7.39 – 7.33 (m, 6H), 7.12 (tt, *J* = 7.5, 1.4 Hz, 1H), 6.73 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 199.1 (quat), 147.9 (quat), 140.5 (quat), 139.7 (quat), 134.9 (CH), 134.1 (CH), 131.3 (CH), 129.4 (2 CH), 129.3 (2 CH), 128.1 (CH), 123.5 (CH), 122.1 (2 CH), 119.7 (quat), 116.5 (CH), 114.6 (CH); HRMS (ES)[–] cald. for (M-H)[–] C₁₉H₁₄NO: 272.1070, found: 272.1071.

[2-(4-Iodo-phenylamino)-phenyl]-(11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-

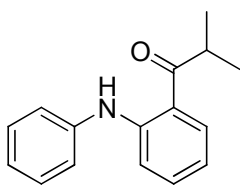


tetraen-1-yl) –methanone (107). Prepared according to

the general procedure A using the corresponding amide (97 mg), TBAT (540 mg) and **9** (261 μL, 2.8 equiv.). Column system: hexane to hexane/DCM (4:6). Isolated as a yellow solid, m = 95 mg. Yield: 82%. M.p. (hexane) 78 °C. R_f

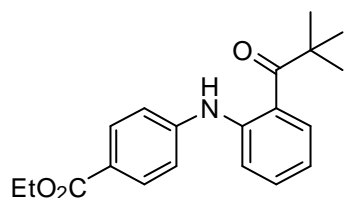
[hexane / DCM (1:1)] = 0.30 ¹H NMR (360 MHz, CDCl₃) δ 10.46 (s, 1H), 8.07 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.66(d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 5.4 Hz, 1H), 7.36 – 7.26 (m, 4H), 7.12 (dd, *J* = (5.4, 1.9 Hz, 1H), 7.08 – 6.96 (m, 4H), 6.69 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 5.91 (d, *J* = 1.9 Hz, 1H). ¹³C NMR (90 MHz, CDCl₃) δ 196.2 (quat), 149.5 (quat), 148.1(quat), 148.1 (quat), 143.7 (CH), 142.9 (CH), 140.0 (quat), 138.4 (2 CH), 135.1 (CH), 134.3 (CH), 125.6 (CH), 125.2 (CH), 124.6 (2 CH), 120.6 (CH), 120.4 (CH), 117.6 (quat), 117.0 (CH), 114.4 (CH), 96.1 (quat), 86.8 (quat), 82.8 (CH); HRMS (ES⁺) cald. for (M)⁺ C₂₃H₁₆INO₂: 465.0220, found: 465.0223.

2-Methyl-1-(2-phenylamino-phenyl)-propan-1-one (108). Prepared according to



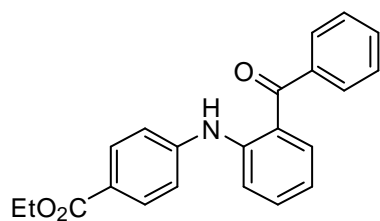
the general procedure A using the corresponding amide (41 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, m = 14 mg. Yield: 23%. Rf [hexane / DCM (1:1)] = 0.58. ^1H NMR (360 MHz, CDCl_3) δ 10.65 (s, 1H), 7.88 (dtd, J = 8.4, 1.2, 0.7, 1H), 7.37 – 7.29 (m, 4H), 7.26 (dd, J = 8.5, 1.1 Hz, 2H), 7.09 (ddd, J = 8.5, 7.3, 1.2 Hz, 1H), 6.74 (m, 1H), 3.67 (sept., J = 6.8 Hz, 1H), 1.25 (d, J = 6.8 Hz, 6H); ^{13}C NMR (90 MHz, CDCl_3) δ 207.6 (quat), 148.3 (quat), 134.2 (CH), 131.4 (CH), 129.3 (2 CH), 123.7 (CH), 122.8 (2 CH), 117.8 (quat), 116.5 (CH), 114.6 (CH), 35.6 (CH), 19.7 (CH_3); HRMS (EI^+) cald. for $(\text{M}+\text{H})^+$ $\text{C}_{16}\text{H}_{18}\text{NO}$: 240.1383; found 240.1386.

4-[2-(2,2-Dimethyl-propionyl)-phenylamino]-benzoic acid ethyl ester (111a).



Prepared according to the general procedure A using the corresponding amide (63 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (3:7). Isolated as a yellow oil, m = 58 mg. Yield: 71%. Rf [hexane / DCM (4:6)] = 0.28. ^1H NMR (360 MHz, CDCl_3) δ 8.51 (s, 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.69 (dd, J = 7.9, 1.5 Hz, 1H), 7.49 (dd, J = 8.3, 1.1 Hz, 1H), 7.33 (ddd, J = 8.7, 7.3, 1.6 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.95 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (90 MHz, CDCl_3) δ 211.6 (quat), 166.3 (quat), 146.5 (quat), 141.6 (quat), 131.5 (CH), 131.2 (2 CH), 129.0 (CH), 126.7 (quat), 122.7 (quat), 120.0 (CH), 119.3 (CH), 116.9 (2 CH), 60.5 (CH_2), 45.1 (quat), 28.2 (CH_3), 14.4 (CH_3); HRMS (ES^+) cald. for $(\text{M}+\text{H})^+$ $\text{C}_{20}\text{H}_{24}\text{NO}_3$: 326.1751; found 326.1749.

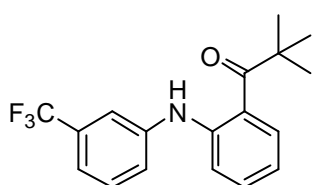
4-(2-Benzoyl-phenylamino)-benzoic acid ethyl ester (111b). Prepared according to



the general procedure A using the corresponding amide (67 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (3:7). Isolated as a yellow oil, m = 73 mg. Yield: 85%. Rf [hexane / DCM (4:6)] = 0.25. ^1H NMR (360 MHz,

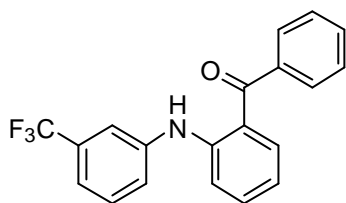
CDCl₃) δ 9.96 (s, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.62 (dd, J = 8.3, 1.4 Hz, 2H), 7.48 – 7.44 (m, 3H), 7.38 (d, J = 7.6 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.74 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H), 4.24 (q, J = 7.13 Hz, 2H), 1.27 (t, J = 7.13 Hz, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 199.9 (quat), 166.2 (quat), 145.4 (quat), 145.2 (quat), 139.1 (quat), 134.6 (CH), 133.9 (CH), 131.9 (CH), 131.2 (2 CH), 129.7 (2 CH), 128.2 (2 CH), 123.7 (quat), 122.1 (quat), 118.6 (CH), 118.5 (2 CH), 116.5 (CH), 60.6 (CH₂), 14.4 (CH₃); HRMS (ES⁺) cald. for (M)⁺ C₂₂H₁₉NO₃: 345.1359, found: 345.1357.

2,2-Dimethyl-1-[2-(3-trifluoromethyl-phenylamino)-phenyl]-propan-1-one



(**112a**). Prepared according to the general procedure A using the corresponding amide (61 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, m = 49 mg. Yield: 61%. Rf [hexane / DCM (1:1)] = 0.65. ¹H NMR (360 MHz, CDCl₃) δ 8.88 (s, 1H), 7.79 (dd, J = 7.9, 1.4 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.34 – 7.28 (m, 2H), 7.23 – 7.21 (m, 1H), 6.89 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 211.2 (quat), 143.6 (quat), 142.4 (quat), 132.0 (CH), 131.8 (q, J = 32.1 Hz, quat), 129.8 (CH), 129.7 (CH), 124.3 (quat), 122.8 (CH), 118.7 (CH), 118.4 (q, J = 3.7 Hz, CH), 117.2 (CH), 116.1 (q, J = 3.7 Hz, CH), 45.1 (quat), 28.5 (CH₃); HRMS (ES⁺) cald. for (M)⁺ C₁₈H₁₈F₃NO: 321.1335; found 321.1335.

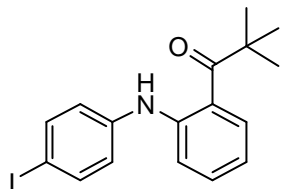
Phenyl-[2-(3-trifluoromethyl-phenylamino)-phenyl]-methanone (**112b**). Prepared



according to the general procedure A using the corresponding amide (66 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow solid, m = 65 mg. Yield: 76%. M.p. (hexane) 44°C. Rf [hexane / DCM (1:1)] = 0.58. ¹H NMR (360 MHz, CDCl₃) δ 10.15 (s, 1H), 7.75 (dd, J = 8.3, 1.4 Hz, 2H), 7.61 - 7.56 (m, 3H), 7.52 – 7.48 (m, 2H), 7.46 – 7.41 (m, 4H), 7.33 – 7.30 (m, 1H), 6.83 (ddd, J = 8.1, 5.8, 2.5 Hz, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 199.0 (quat), 144.5 (quat), 141.5 (quat), 139.3 (quat), 134.8 (CH), 134.1 (CH), 131.8 (q, J = 32.3 Hz, quat),

131.7 (CH), 129.9 (CH), 129.5 (2 CH), 128.1 (2 CH), 124.1 (CH), 120.9 (quat), 119.3 (q, $J = 3.6$ Hz, CH), 117.9 (CH), 117.5 (q, $J = 3.7$ Hz, CH), 115.0 (CH); HRMS (ES⁻) cald. for (M-H)⁻ C₂₀H₁₃F₃NO: 340.0944; found 340.0945.

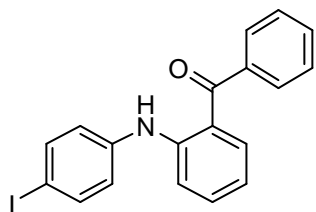
1-[2-(4-Iodo-phenylamino)-phenyl]-2,2-dimethyl-propan-1-one (113a). Prepared



according to the general procedure A using the corresponding amide (76 mg), TBAT (270 mg) and **9** (93 μL). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow solid, m = 65 mg. Yield: 69%. M.p. (hexane) 82 °C. R_f [hexane / DCM (6:4)] = 0.54. ¹H NMR (360 MHz, CDCl₃) δ

8.79 (s, 1H), 7.76 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.56 (d, $J = 8.7$ Hz, 2H), 7.34 – 7.25 (m, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.83 (ddd, $J = 8.2, 7.0, 1.3$ Hz, 1H), 1.38 (s, 9H); ¹³C NMR (90 MHz, CDCl₃) δ 211.0 (quat), 144.1 (quat), 141.5 (quat), 138.1 (2 CH), 131.9 (CH), 129.7 (CH), 123.7 (quat), 122.1 (2 CH), 118.1 (CH), 117.1 (CH), 84.3 (quat), 45.0 (quat), 28.5 (CH₃); HRMS (ES⁺) cald. for (M)⁺ C₁₇H₁₈INO: 379.0429; found 379.0428.

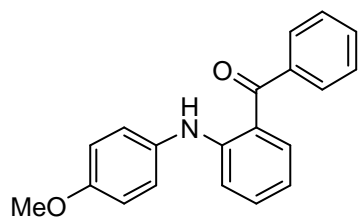
[2-(4-Iodo-phenylamino)-phenyl]-phenyl-methanone (113b). Prepared according



to the general procedure A using the corresponding amide (81 mg), TBAT (270 mg) and **9** (93 μL). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, m = 81 mg. Yield: 81%. R_f [hexane / DCM (6:4)] = 0.40. ¹H NMR (360 MHz, CDCl₃) δ 10.04 (s, 1H), 7.72 (dd, $J = 8.3,$

1.4 Hz, 2H), 7.63 (d, $J = 8.7$ Hz, 2H), 7.57 – 7.54 (m, 2H), 7.48 (t, $J = 7.3$ Hz, 2H), 7.38 – 7.36 (m, 2H), 7.06 (d, $J = 8.8$ Hz, 2H), 6.76 (ddd, $J = 8.1, 5.4, 2.9$ Hz, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 199.0 (quat), 146.9 (quat), 140.5 (quat), 139.4 (quat), 138.2 (2 CH), 134.8 (CH), 134.1 (CH), 131.6 (CH), 129.4 (2 CH), 128.1 (2 CH), 123.4 (2 CH), 120.4 (quat), 117.3 (CH), 114.8 (CH), 85.7 (quat); HRMS (ES)⁺ cald. for (M+H)⁺ C₁₉H₁₅INO: 400.0193, found: 400.0189.

[2-(4-Methoxy-phenylamino)-phenyl]-phenyl-methanone (114). Prepared

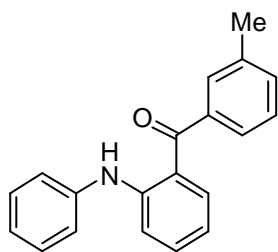


according to the general procedure A using the corresponding amide (57 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (3:7).

Isolated as an orange oil, m = 49 mg. Yield: 65%. Rf [hexane / DCM (4:6)] = 0.42. ^1H NMR (360 MHz, CDCl_3) δ 10.07 (s, 1H), 7.69 (dd, J = 8.2, 1.5 Hz, 2H), 7.57 – 7.46 (m, 4H), 7.29 (ddd, J = 8.6, 7.0, 1.6 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 7.10 (dd, J = 8.6, 1.0 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 6.63 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 3.83 (s, 3H); ^{13}C

NMR (90 MHz, CDCl_3) δ 199.2 (quat), 156.7 (quat), 149.9 (quat), 140.1 (quat), 135.1 (CH), 134.4 (CH), 133.1 (quat), 131.0 (CH), 129.2 (2 CH), 128.1 (2 CH), 125.6 (2 CH), 118.3 (quat), 115.5 (CH), 114.7 (2 CH), 113.8 (CH), 55.5 (CH_3); HRMS (ES) $^+$ cald. for (M+H) $^+$ $\text{C}_{20}\text{H}_{18}\text{NO}_2$: 304.1332, found: 304.1334.

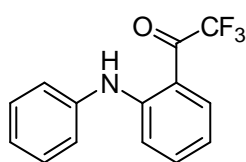
(2-Phenylamino-phenyl)-*m*-tolyl-methanone (115). Prepared according to the



general procedure A using the corresponding amide (53 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, m = 63 mg. Yield: 88%. Rf [hexane / DCM (1:1)] = 0.60. ^1H NMR (360 MHz, CDCl_3) δ 10.14 (s, 1H), 7.58 – 7.49 (m, 3H), 7.41 –

7.30 (m, 8H), 7.11 (dt, J = 7.2, 1.3 Hz, 1H), 6.72 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H); ^{13}C NMR (90 MHz, CDCl_3) δ 199.4 (quat), 147.9 (quat), 140.6 (quat), 139.8 (quat), 137.9 (quat), 135.0 (CH), 134.1 (CH), 132.1 (CH), 129.8 (CH), 129.3 (2 CH), 127.9 (CH), 126.6 (CH), 123.4 (CH), 122.1 (2 CH), 119.9 (quat), 116.5 (CH), 114.6 (CH), 21.3 (CH_3); HRMS (ES) $^+$ cald. for (M+H) $^+$ $\text{C}_{20}\text{H}_{18}\text{NO}$: 288.1383, found: 288.1383.

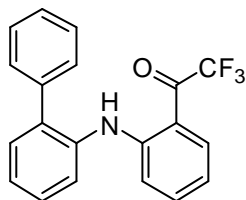
2,2,2-Trifluoro-1-(2-phenylamino-phenyl)-ethanone (116a). Prepared according to



the general procedure A using the corresponding amide (47 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (8:2). Isolated as a yellow oil, m = 66 mg. Yield: 99%. Rf [hexane / DCM (8:2)] = 0.50 ^1H NMR (360 MHz, CDCl_3) δ 10.24 (s, 1H), 7.89 – 7.84 (m, 1H), 7.44 – 7.37 (m, 3H), 7.29 – 7.20 (m,

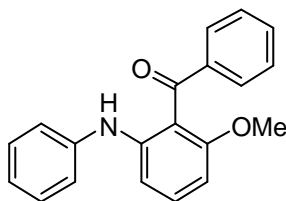
4H), 6.77 (ddd, $J = 8.1, 7.0, 1.0$ Hz, 1H). The spectroscopic data was in agreement with that previously published.⁶⁷

1-[2-(Biphenyl-2-ylamino)-phenyl]-2,2,2-trifluoro-ethanone (116b). Prepared



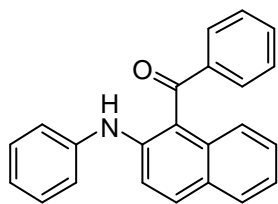
according to the general procedure A using the corresponding amide (67 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (8:2). Isolated as an orange oil, $m = 77$ mg. Yield: 90%. R_f [hexane / DCM (85:15)] = 0.40. ^1H NMR (360 MHz, CDCl_3) δ 9.99 (s, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.46 – 7.29 (m, 10H), 7.09 (d, $J = 8.7$ Hz, 1H), 6.71 (ddd, $J = 8.1, 7.3, 0.9$ Hz, 1H); ^{13}C NMR (90 MHz, CDCl_3) δ 180.6 (q, $J = 33.3$ Hz, quat), 151.4 (quat), 138.5 (quat), 137.8 (quat), 136.6 (CH), 136.2 (quat), 131.7 (dd, $J = 8.1, 4.0$ Hz, CH), 131.3 (CH), 128.9 (2 CH), 128.4 (2 CH), 128.3 (CH), 127.6 (CH), 126.1 (CH), 125.6 (CH), 116.7 (CH), 114.8 (CH), 112.0 (quat); HRMS (ES)⁺ cald. for (M+H)⁺ $\text{C}_{20}\text{H}_{15}\text{F}_3\text{NO}$: 342.1100, found: 342.1099.

(2-Methoxy-6-phenylamino-phenyl)-phenyl-methanone (117). Prepared according



to the general procedure A using the corresponding amide (49 mg), TBAT (270 mg) and **29** (100 μ L). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, $m = 49$ mg. Yield: 65%. R_f [hexane / DCM (1:1)] = 0.40. ^1H NMR (360 MHz, CDCl_3) δ 7.38 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.56 – 7.52 (m, 2H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.31 – 7.27 (m, 3H), 7.14 (dd, $J = 8.6, 1.1$ Hz, 2H), 7.05 (dd, $J = 8.4, 0.6$ Hz, 1H), 6.98 (ddd, $J = 8.5, 7.3, 1.1$ Hz, 1H), 6.48 (dd, $J = 8.2, 0.7$ Hz, 1H), 3.59 (s, 3H); ^{13}C NMR (90 MHz, CDCl_3) δ 198.7 (quat), 144.4 (quat), 141.7 (quat), 139.5 (quat), 132.5 (CH), 132.1 (CH), 129.1 (2 CH), 128.9 (2 CH), 128.1 (2 CH), 122.0 (CH), 119.9 (2 CH), 115.6 (quat), 109.4 (CH), 102.4 (CH), 55.4 (CH_3); HRMS (ES)⁺ cald. for (M+H)⁺ $\text{C}_{20}\text{H}_{18}\text{NO}_2$: 304.1332; found 304.1332.

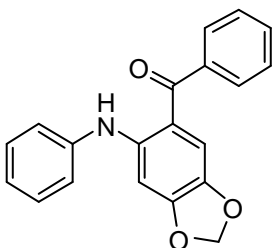
Phenyl-(2-phenylamino-naphthalen-1-yl)-methanone (118). Prepared according to



the general procedure A using the corresponding amide (49 mg), TBAT (270 mg) and the corresponding benzyne precursor (121 μ L). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, m = 63 mg. Yield: 78%. Rf [hexane / DCM (1:1)] = 0.50. ^1H NMR (360 MHz, CDCl_3) δ

7.79 – 7.75 (m, 3H), 7.71 (dd, J = 7.7, 1.4 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.50 (ddd, J = 8.7, 7.4, 1.3 Hz, 1H), 7.46 (s, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.30 (dd, J = 8.2, 0.8 Hz, 1H), 7.26 – 7.17 (m, 4H), 7.07 (dd, J = 8.6, 1.1 Hz, 2H), 6.95 (ddd, J = 8.5, 7.4, 1.1 Hz, 1H); ^{13}C NMR (90 MHz, CDCl_3) δ 198.0 (quat), 141.8 (quat), 141.1 (quat), 139.0 (quat), 133.3 (CH), 132.6 (quat), 131.7 (CH), 129.8 (2 CH), 129.3 (2 CH), 128.6 (2 CH), 128.6 (quat), 128.1 (CH), 126.7 (CH), 125.5 (CH), 123.6 (CH), 122.3 (CH), 120.6 (quat), 119.7 (2 CH), 118.7 (CH); HRMS (ES^+) calcd. for $(\text{M}+\text{H})^+$ $\text{C}_{23}\text{H}_{18}\text{NO}$: 324.1383; found 324.1382.

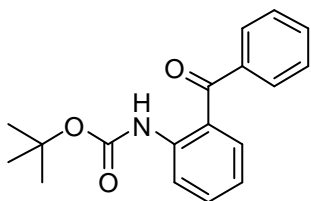
Phenyl-(6-phenylamino-benzo[1,3]dioxol-5-yl)-methanone (119). Prepared



according to the general procedure A using the corresponding amide (49 mg), TBAT (270 mg) and **15** (115 μ L). Column system: hexane to hexane/DCM (1:1). Isolated as a yellow oil, m = 60 mg. Yield: 76%. Rf [hexane / DCM (4:6)] = 0.66. ^1H NMR (360 MHz, CDCl_3) δ 10.82 (s, 1H), 7.64 (dd, J = 8.1,

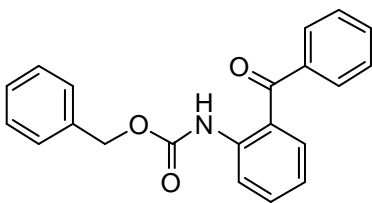
1.6 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.37 (dd, J = 8.4, 7.3 Hz, 2H), 7.28 (dd, J = 8.5, 1.0 Hz, 2H), 7.12 (ddd, J = 8.5, 7.3, 1.0 Hz, 1H), 6.96 (s, 1H), 6.86 (s, 1H), 5.91 (s, 2H); ^{13}C NMR (90 MHz, CDCl_3) δ 197.0 (quat), 153.2 (quat), 147.6 (quat), 140.5 (quat), 140.4 (quat), 138.7 (quat), 130.7 (CH), 129.4 (2 CH), 128.8 (2 CH), 128.1 (2 CH), 123.8 (CH), 122.6 (2 CH), 112.2 (CH), 111.9 (quat), 101.4 (CH_2), 94.9 (CH); HRMS (ES^+) calcd. for $(\text{M}+\text{H})^+$ $\text{C}_{20}\text{H}_{15}\text{NO}_3$: 318.1125; found 318.11

(2-Benzoyl-phenyl)-carbamic acid *tert*-butyl ester (121a). Prepared according to



the general procedure A using the corresponding amide (56 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (4:6). Isolated as a colourless oil, $m = 52$ mg. Yield: 70%. M.p. (hexane) 94 $^{\circ}$ C; R_f [hexane / DCM (1:1)] = 0.42. ^1H NMR (360 MHz, CDCl_3) δ 10.06 (s, 1H), 8.42 (d, $J = 8.2$, 1H), 6.69 (d, $J = 6.9$, 2H), 7.58 – 7.43 (m, 5H), 6.99 (t, $J = 7.6$ Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (90 MHz, CDCl_3) δ 199.2 (quat), 141.3 (quat), 138.8 (quat), 134.0 (CH), 133.4 (CH), 129.8 (2 CH), 128.2 (2 CH), 122.7 (quat), 120.6 (CH), 119.8 (CH), 80.5 (quat), 28.2 (CH_3); HRMS (ES^+) calcd. for $(\text{M}+\text{H})^+$ $\text{C}_{18}\text{H}_{20}\text{NO}_3$: 298.1438; found 298.1440.

(2-Benzoyl-phenyl)-carbamic acid benzyl ester (121b). Prepared according to the



general procedure A using the corresponding amide (68 mg), TBAT (270 mg) and **9** (93 μ L). Column system: hexane to hexane/DCM (4:6). Isolated as a colourless oil, $m = 65$ mg. Yield: 75%. R_f [hexane / DCM (1:1)] = 0.38. ^1H NMR (360 MHz, CDCl_3) δ 10.36 (s, 1H), 8.46 (d, $J = 8.4$, 1H), 7.69 (dd, $J = 8.3$, 1.3 Hz, 2H), 7.61 – 7.53 (m, 3H), 7.49 – 7.31 (m, 7H), 7.04 (dt, $J = 7.9$, 1.1 Hz, 1H), 5.23 (s, 2H); ^{13}C NMR (90 MHz, CDCl_3) δ 199.2 (quat), 153.6 (quat), 140.8 (quat), 138.6 (quat), 136.0 (quat), 134.1 (CH), 133.5 (CH), 132.3 (CH), 129.8 (2 CH), 128.5 (2 CH), 128.2 (2 CH), 128.1 (3 CH), 122.8 (quat), 121.1 (CH), 119.9 (CH), 66.9 (CH_2). HRMS (ES^+) calcd. for $(\text{M}+\text{NH}_4)^+$ $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3$: 349.1547; found 349.1547.

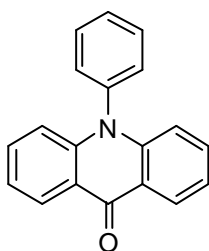
1.4.4 Procedure B for the synthesis of *N*-phenyl acridones

To a solution of the *o*-halobenzamides (0.250 mmol) and TBAT (0.750 mmol) in toluene (3 mL) was added the aryne precursor (0.750 mmol). The sealed tube was heated for 5 min at 120 $^{\circ}$ C in a microwave and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel to afford the desired product.

Microwave parameters:

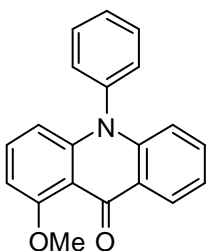
All microwave experiments were carried out in a 5 mL vial using a Biotage Initiator™ instrument. The solutions were pre-stirred for 20 seconds before the irradiation began. The absorbance of the solvent was set as “normal”. The reaction time was initiated as soon the system reached the input temperature, although approximately two minutes were needed to reach it. The average power of the reaction was 75 W.

***N*-Phenyl acridone (127).**



Prepared according to the general procedure B using the amide **126** (54 mg), TBAT (404 mg) and **9** (186 μ L). Column system: hexane/DCM (1:1) to DCM/EtOAc (9:1). Isolated as a white solid, m = 62 mg. Yield: 92%. M.p. (DCM) = 266 °C; Rf [DCM:EtOAc (9:1)] = 0.63. ^1H NMR (360 MHz, CDCl_3) δ 8.60 (dd, J = 7.9, 1.0 Hz, 2H), 7.74 – 7.66 (m, 3H), 7.77 (ddd, J = 8.5, 7.1, 1.4 Hz, 2H), 7.38 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.4 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H); ^{13}C NMR (90 MHz, CDCl_3) δ 178.1 (quat), 143.1 (quat), 138.9 (quat), 133.2 (2 CH), 131.0 (2 CH), 130.0 (2 CH), 129.6 (CH), 127.2 (2 CH), 121.8 (quat), 121.5 (2 CH), 116.8 (2 CH); HRMS (ES)⁺ calcd. for (M+H)⁺ $\text{C}_{19}\text{H}_{14}\text{NO}$: 272.1070, found: 272.1074.

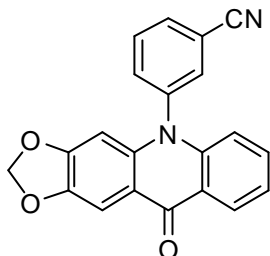
***1*-methoxy-10-phenylacridin-9(10H)-one (128).** Prepared according to the general



procedure B using the amide **126** (54 mg), TBAT (404 mg) and **29** (205 μ L). Column system: hexane/DCM (1:1) to DCM/EtOAc (8:2). Isolated as a white solid, m = 47 mg. Yield: 62%. M.p. (DCM) = 222 °C; Rf [DCM / EtOAc (85:15)] = 0.40. ^1H NMR (360 MHz, CDCl_3) δ 8.55 (d, J = 8.0 Hz, 1H), 7.71 – 7.63 (m, 3H), 7.42 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.36 – 7.32 (m, 3H), 7.23 (t, J = 7.5 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 8.6 Hz, 1H), 6.28 (d, J = 8.7 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (90 MHz, CDCl_3) δ 177.8 (quat), 161.5 (quat), 145.7 (quat), 142.3 (quat), 139.6 (quat), 133.2 (CH), 132.6 (CH), 131.0 (2 CH), 130.1 (2 CH), 129.4 (CH), 127.4 (CH), 123.6 (quat), 121.5 (CH), 116.8 (CH), 112.6 (quat),

109.1 (CH), 102.7 (CH), 56.3 (CH₃); HRMS (ES)⁺ cald. for (M+H)⁺ C₂₀H₁₆NO₂: 302.1176, found: 302.1175.

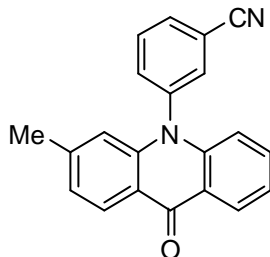
3-(10-Oxo-10H-[1,3]dioxolo[4,5-b]acridin-5-yl)-benzonitrile (130). Prepared



according to the general procedure B using the amide **129** (60 mg), TBAT (404 mg) and **15** (214 μ L). Column system: hexane/DCM (1:1) to DCM/EtOAc (8:2). Isolated as a white solid, m = 76 mg. Yield: 89%. M.p. (DCM) = 310 °C; R_f [DCM / EtOAc (85:15)] = 0.48. ¹H NMR (360 MHz, DMSO-*d*₆) δ 8.36 (d, *J* = 8.0 Hz, 1H), 8.25 – 8.23 (m, 2H), 8.03 – 7.94 (m, 2H), 7.70 (s, 1H), 7.62 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.2 – 6.1 (m, 3H); ¹³C NMR (90 MHz, DMSO-*d*₆) δ 175.9 (quat), 153.9 (quat), 145.0 (quat), 142.9 (quat), 141.2 (quat), 140.3 (quat), 136.4 (CH), 135.0 (CH), 134.9 (CH), 134.1 (CH), 133.7 (CH), 127.1 (CH), 122.8 (CH), 121.5 (quat), 118.8 (quat), 117.7 (CH), 117.0 (quat), 115.4 (quat), 103.6 (CH), 103.4 (CH₂), 97.2 (CH); HRMS (ES)⁺ cald. for (M)⁺ C₂₁H₁₂N₂O₃: 340.08424, found: 340.08408.

Structure of regioisomers **132a** and **132b** were assigned on the basis of the ¹H NMR chemical shift of the singlet adjacent to the methyl group in the acridone. For **132a**, the singlet at C4 is at δ = 6.36, *ortho* to the nitrogen atom (EDG). For **132b**, the singlet at C1 is deshielded by the *ortho* carbonyl group and appears at δ = 8.32. For analogous acridones to **132b** in the literature, see: Smith, J. A.; West, R. M.; Allen, M. J. *Fluorescence*, 2004, 14, 151-191 (compound **19**)¹²⁶ and Nishio, R.; Wessely, S.; Sugiura, M.; Kobayashi, S. *J. Comb. Chem.* 2006, 8, 459-461 (compound **8ab**).¹¹³

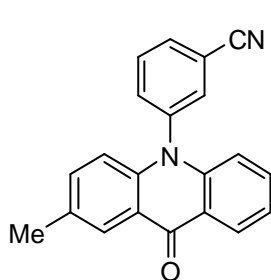
3-(3-methyl-9-oxoacridin-10(9H)-yl)benzonitrile (132a). Prepared according to the



general procedure B using the amide **129** (60 mg), TBAT (404 mg) and **131** (195 μ L). Column system: hexane/DCM (1:1) to DCM/EtOAc (8:2). Isolated as a white solid, m = 32 mg. Yield: 43%. M.p. (DCM) = 298 °C; R_f [DCM / EtOAc (85:15)] = 0.62. ¹H NMR (360 MHz, CDCl₃) δ 8.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.48 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.88 (t, *J* = 7.8

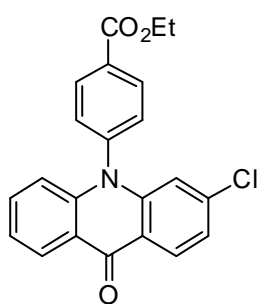
Hz, 1H), 7.73 (s, 1H), 7.67 (d, $J = 7.9$ Hz, 1H), 7.51 (ddd, $J = 8.7, 7.1, 1.5$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.14 (d, $J = 8.1$ Hz, 1H), 6.58 (d, $J = 8.6$ Hz, 1H), 6.36 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (90 MHz, CDCl_3) δ 177.7 (quat), 144.8 (quat), 142.8 (quat), 142.6 (quat), 140.1 (quat), 135.4 (CH), 134.2 (CH), 133.4 (CH), 133.3 (CH), 132.3 (CH), 130.5 (quat), 127.7 (CH), 127.6 (CH), 123.9 (CH), 122.0 (CH), 120.0 (quat), 117.3 (quat), 116.0 (CH), 115.7 (CH), 115.6 (quat), 22.3 (CH_3); HRMS (ES) $^+$ cald. for (M) $^+$ $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}$: 310.11006, found: 310.10995.

3-(2-methyl-9-oxoacridin-10(9H)-yl)benzonitrile (132b) Prepared according to the



general procedure B using the amide **129** (60 mg), TBAT (404 mg) and **131** (195 μL). Column system: hexane/DCM (1:1) to DCM/EtOAc (8:2). Isolated as a white solid, m = 32 mg. Yield: 42%. M.p. (DCM) = 272 $^\circ\text{C}$; Rf [DCM / EtOAc (85:15)] = 0.72. ^1H NMR (360 MHz, CDCl_3) δ 8.52 (dd, $J = 8.0, 1.3$ Hz, 1H), 8.32 (s, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 7.82 (t, $J = 7.9$ Hz, 1H), 7.68 (s, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.46 (ddd, $J = 8.5, 7.1, 1.5$ Hz, 1H), 7.30 (dd, $J = 8.7, 2.0$ Hz, 1H), 7.24 (t, $J = 7.6$ Hz, 1H), 6.56 (d, $J = 8.6$ Hz, 1H), 6.48 (d, $J = 8.7$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (90 MHz, CDCl_3) δ 177.9 (quat), 142.5 (quat), 140.8 (quat), 140.2 (quat), 135.4 (CH), 135.0 (CH), 134.1 (CH), 133.5 (CH), 133.2 (CH), 132.2 (CH), 131.9 (quat), 127.7 (CH), 126.9 (CH), 121.8 (CH), 121.8 (quat), 121.7 (quat), 117.2 (quat), 116.0 (CH), 115.9 (CH), 115.6 (quat), 20.7 (CH_3); HRMS (ES) $^+$ cald. for (M) $^+$ $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}$: 310.11006, found: 310.11026.

4-(3-Chloro-9-oxo-9H-acridin-10-yl)-benzoic acid ethyl ester (134). Prepared



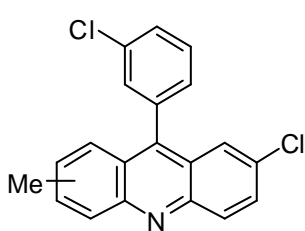
according to the general procedure B using the amide **133** (84 mg), TBAT (404 mg) and **9** (186 μL). Column system: hexane/DCM (1:1) to DCM/EtOAc (9:1). Isolated as a white solid, m = 83 mg. Yield: 88%. M.p. (DCM) = 257 $^\circ\text{C}$; Rf (DCM) = 0.19. ^1H NMR (360 MHz, CDCl_3) δ 8.54 (dd, $J = 8.1, 1.6$ Hz, 1H), 8.50 (d, $J = 8.6$ Hz, 1H), 8.42 (d, $J = 8.4$ Hz, 2H), 7.54 – 7.47 (m, 3H), 6.30 (t, $J = 7.6$ Hz, 1H), 7.23 (dd, $J = 8.6, 1.8$ Hz, 1H), 6.70 – 6.67 (m, 2H), 4.50 (q, $J = 7.1$ Hz, 2H), 1.48 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (90

MHz, CDCl₃) δ 177.2 (quat), 165.4 (quat), 143.3 (quat), 142.7 (quat), 142.3 (quat), 139.9 (quat), 133.7 (CH), 132.6 (2 CH), 132.2 (quat), 130.2 (2 CH), 129.2 (CH), 127.4 (CH), 122.5 (CH), 122.3 (CH), 121.9 (quat), 120.2 (quat), 116.6 (CH), 116.0 (CH), 61.7 (CH₂), 14.3 (CH₃); HRMS (ES⁺) cald. for (M)⁺ C₂₂H₁₆NO₃Cl: 377.0813, found: 377.0808.

1.4.5 Procedure C for the synthesis of 9-phenyl acridines

To a microwave vial (2 – 5 mL) containing a solution of the amide (0.250 mmol) and TBAT (0.500 mmol) in toluene (3 mL) was added the aryne precursor (0.425 mmol) using a syringe. The reaction vessel was sealed with a serum septum and flushed for 2 min with nitrogen using a balloon of N₂. Then, the reaction was heated at 50 °C for 16 h. At room temperature, boron trifluoride diethyl etherate (0.500 mmol) was added through the septum using a syringe and the solution heated at 80 °C for 4 h. After cooling to room temperature, ethyl acetate (20 mL) was added to the reaction. The mixture was washed with water (3 × 20 ml), and the organic phase dried over MgSO₄ and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel to afford the desired product.

7-Chloro-9-(3-chloro-phenyl)-2-methyl-4a, 9a-dihydro-acridine and 7-Chloro-9-



(3-chloro-phenyl)-3-methyl-4a, 9a-dihydro-acridine

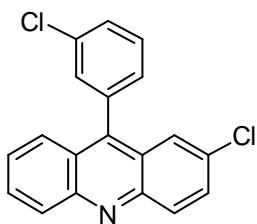
(**135a** and **135b**). Prepared according to the general procedure C using the corresponding amide (66 mg), TBAT (270 mg), **131** (111 μ L) and BF₃.Et₂O (35 μ L).

Column system: hexane/DCM (9:1) to hexane/DCM (1:9).

Isolated as a yellow solid, m = 59 mg. Yield: 67%. M.p. (DCM) = 218 °C; R_f (DCM) = 0.60. ¹H NMR (360 MHz, CDCl₃) δ 8.20 – 8.01 (m, 2H), 7.68 – 7.51 (m, 5H), 7.43 (s, 1H), 7.33 – 7.29 (m, 2H), 2.60 (s, 1.58H), 2.46 (s, 1.41H); ¹³C NMR (90 MHz, CDCl₃) δ 148.9 (quat), 147.6 (quat), 146.8 (quat), 146.2 (quat), 144.1 (quat), 143.2 (quat), 141.0 (quat), 137.3 (quat), 137.1 (quat), 136.7 (quat), 134.7 (quat), 133.3

(CH), 131.7 (quat), 131.3 (CH), 131.1 (2 CH), 130.8 (CH), 130.2 (CH), 130.0 (2 CH), 129.5 (CH), 129.3 (CH), 128.8 (2 CH), 128.5 (CH), 127.9 (CH), 125.9 (CH), 125.3 (quat), 125.1 (quat), 124.8 (quat), 124.6 (CH), 124.5 (CH), 124.2 (CH), 123.4 (quat), 22.2 (CH₃), 22.1 (CH₃); HRMS (ES⁺) cald. for (M+H)⁺ C₂₀H₁₄NCl₂: 338.0498, found: 338.0499.

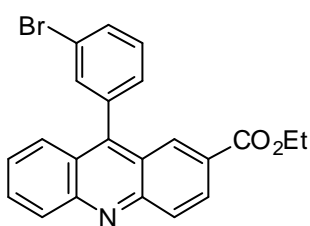
7-Chloro-9-(3-chloro-phenyl)-4a,9a-dihydro-acridine (136). Prepared according



to the general procedure C using the corresponding amide (66 mg), TBAT (270 mg), **9** (106 μL) and BF₃.Et₂O (35 μL). Column system: hexane/DCM (9:1) to hexane/DCM (1:9). Isolated as a yellow solid, m = 63 mg. Yield: 78%. M.p. (DCM) = 186 °C; R_f (DCM) = 0.55. ¹H NMR (360 MHz, CDCl₃) δ 8.25 (d, *J* = 8.8 Hz, 1H), 8.21 (d, *J* = 9.2 Hz, 1H), 7.78 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.69 – 7.54 (m, 5H), 7.49 – 7.30 (m, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 148.5 (quat), 146.7 (quat), 144.5 (quat), 137.0 (quat), 134.8 (quat), 131.9 (quat), 131.4 (CH), 131.3 (CH), 130.4 (CH), 130.2 (CH), 130.0 (CH), 129.6 (CH), 128.9 (CH), 128.5 (CH), 126.6 (CH), 126.3 (CH), 125.1 (quat), 125.1 (quat), 124.6 (CH);

HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₁₂NCl₂: 324.0341, found: 324.0343.

9-(3-Bromo-phenyl)-8a, 10a-dihydro-acridine-2-carboxylic acid ethyl ester (137). Prepared according to the general procedure C using

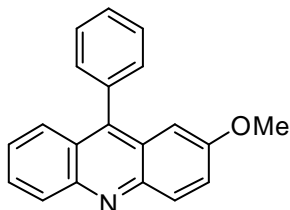


the corresponding amide (89 mg), TBAT (270 mg), **9** (106 μL) and BF₃.Et₂O (35 μL). Column system: hexane/DCM (9:1) to DCM/EtOAc (9:1). Isolated as a yellow solid, m = 73 mg. Yield: 72%. M.p. (DCM) = 215 °C; R_f (DCM) =

0.16. ¹H NMR (360 MHz, CDCl₃) δ 8.46 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.32 – 8.29 (m, 3H), 7.83 (ddd, *J* = 8.7, 6.6, 1.4 Hz, 1H), 7.76 (ddd, *J* = 8.1, 1.9, 1.1 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 1.7 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.43 – 7.39 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 166.0 (quat), 149.8 (quat), 149.5 (quat), 147.5 (quat), 137.1 (quat), 133.1 (CH), 132.0 (CH), 131.2 (CH), 130.3 (CH), 130.2 (CH), 129.9 (CH), 129.7 (CH), 129.1 (CH), 128.9 (CH), 127.8 (quat), 126.7 (CH), 126.5 (CH), 125.1 (quat), 123.8 (quat), 122.8

(quat), 61.4 (CH₂), 14.3 (CH₃); HRMS (ES⁺) cald. for (M+H)⁺ C₂₂H₁₇NO₂Br: 406.0437, found: 406.0439.

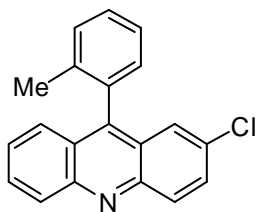
7-Methoxy-9-phenyl-4a,9a-dihydro-acridine (138). Prepared according to the



general procedure C using the corresponding amide (57 mg), TBAT (270 mg), **9** (106 μ L) and BF₃.Et₂O (35 μ L). Column system: hexane/DCM (1:1) to DCM/EtOAc (9:1). Isolated as a yellow solid, m = 44 mg. Yield: 64%. M.p. (DCM) = 84 °C; R_f [DCM/EtOAc (9:1)] = 0.46. ¹H NMR (360 MHz, CDCl₃) δ 8.25 (d, *J* = 8.7 Hz, 1H), 8.19 (d, *J* = 9.4 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.64 – 7.57 (m, 4H), 7.48 – 7.38 (m, 4H), 6.82 (d, *J* = 2.5 Hz, 1H), 3.73 (s, 3H); ¹³C

NMR (90 MHz, CDCl₃) δ 156.8 (quat), 146.9 (quat), 145.7 (quat), 144.8 (quat), 136.2 (quat), 130.9 (CH), 130.2 (2CH), 129.3 (CH), 128.9 (CH), 128.6 (2CH), 128.3 (CH), 126.3 (CH), 125.9 (quat), 125.7 (CH), 125.3 (quat), 125.1 (CH), 101.9 (CH), 55.3 (CH₃); HRMS (ES⁺) cald. for (M+H)⁺ C₂₀H₁₆NO: 286.1226, found: 286.1226.

7-Chloro-9-*o*-tolyl-4a,9a-dihydro-acridine (139). Prepared according to the general

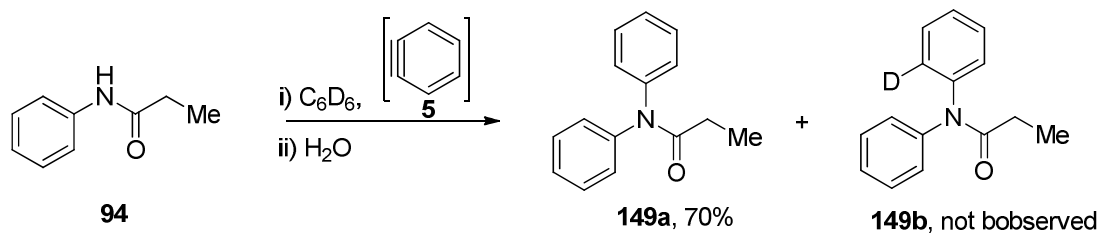


procedure C using the corresponding amide (61 mg), TBAT (270 mg), **9** (106 μ L) and BF₃.Et₂O (35 μ L). Column system: hexane/DCM (9:1) to DCM. Isolated as a yellow solid, m = 56 mg. Yield: 74%. M.p. (DCM) = 155 °C; R_f (DCM) = 0.40. ¹H NMR (360 MHz, CDCl₃) δ 8.27 (d, *J* = 8.8 Hz, 1H), 8.23 (d, *J* = 9.3 Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.69 (dd, *J* = 9.3, 1.6 Hz, 1H), 7.53 – 7.39 (m, 6H), 7.21 (d, *J* = 7.4 Hz, 1H), 1.87 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ

148.8 (quat), 147.0 (quat), 146.3 (quat), 136.8 (quat), 134.7 (quat), 131.6 (quat), 131.4 (CH), 131.3 (CH), 130.4 (CH), 130.3 (CH), 130.1 (CH), 129.7 (CH), 128.9 (CH), 126.5 (CH), 126.4 (CH), 126.0 (quat), 125.4 (quat), 125.3 (quat), 124.7 (CH), 19.8 (CH₃); HRMS (ES⁺) cald. for (M+H)⁺ C₂₀H₁₅NCl: 304.0888, found: 304.0888.

1.4.6 Mechanistic studies

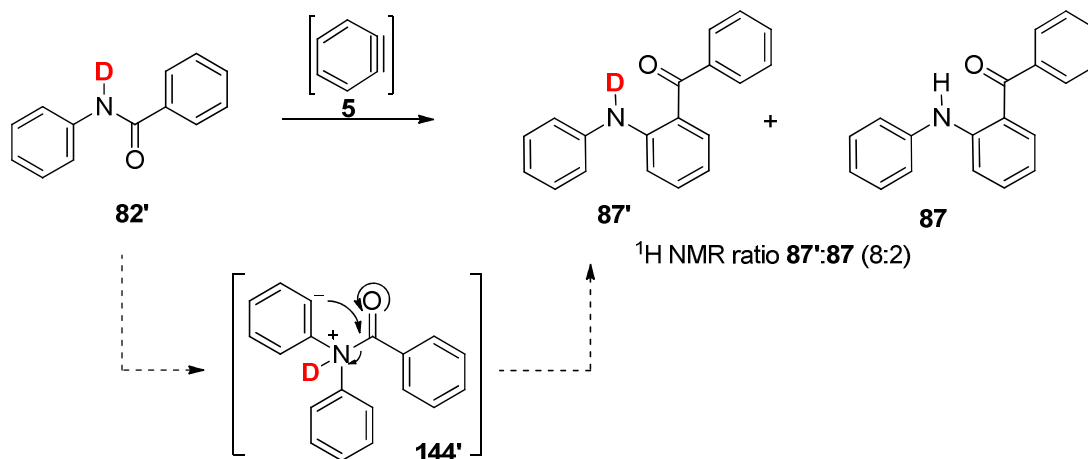
1.4.6.1 Study A: solvent as proton source



Scheme 1.42. Reaction carried out in deuterated solvent.

To a solution of *N*-phenylpropionamide **94** (0.250 mmol) and TBAT (0.500 mmol) in deuterated benzene C₆D₆ (3 mL) was added the benzyne precursor **9** (0.375 mmol). The reaction was heated at 50 °C for 16 h and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel (dry loading) to afford the *N,N*-diphenylpropionamide product **149a** in 70% yield. The spectroscopic data was in agreement with that previously reported.¹²⁷ ¹H, ²H and ¹³C NMR indicated no deuterium incorporation into the product.

1.4.6.2 Study B: identification of the zwitterion intermediate



Scheme 1.43. Identification of the zwitterion intermediate.

To a solution of *N*-deuterated benzanilide **82'** (0.252 mmol) and TBAT (0.429 mmol) in toluene (3 mL) was added the benzyne precursor **9** (0.378 mmol). The

reaction was heated at 50 °C for 16 h and concentrated under reduced pressure. The resulting mixture was triturated with hexane (3 × 5 mL) to remove the *tert*-butyl ammonium salt. The hexane layer were combined and evaporated under vacuo. The crude mixture was analysed by ^1H NMR to determine the percentage of N-D in the product (Figure 1.15).

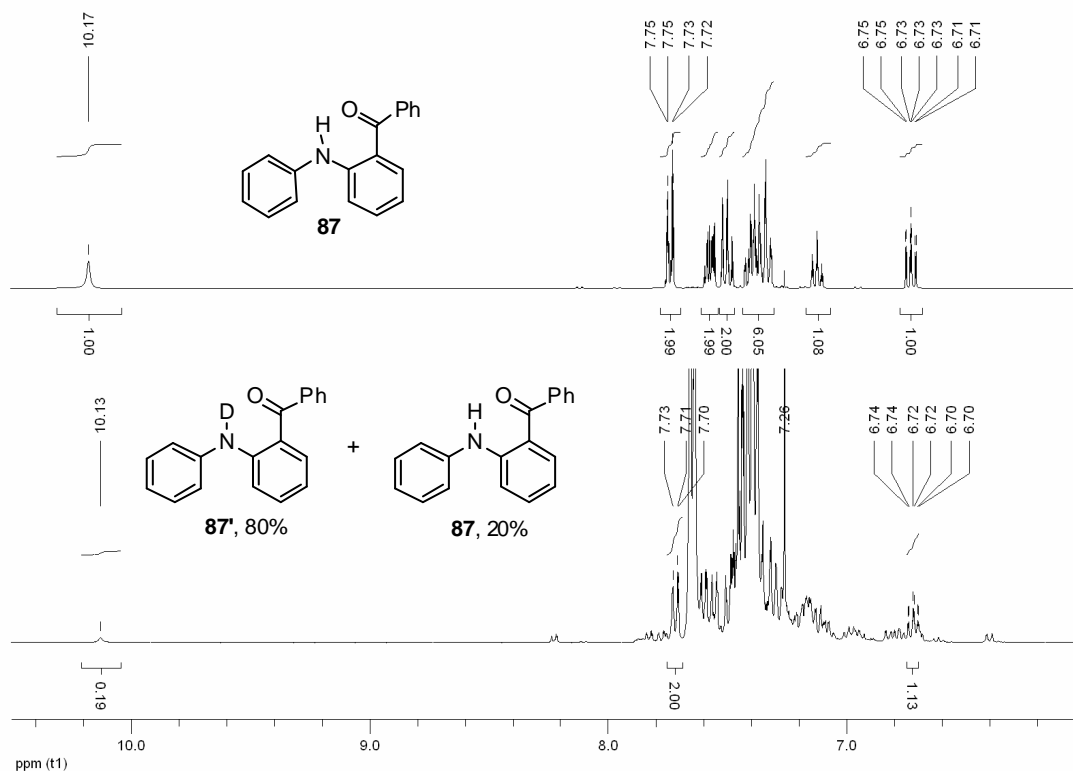
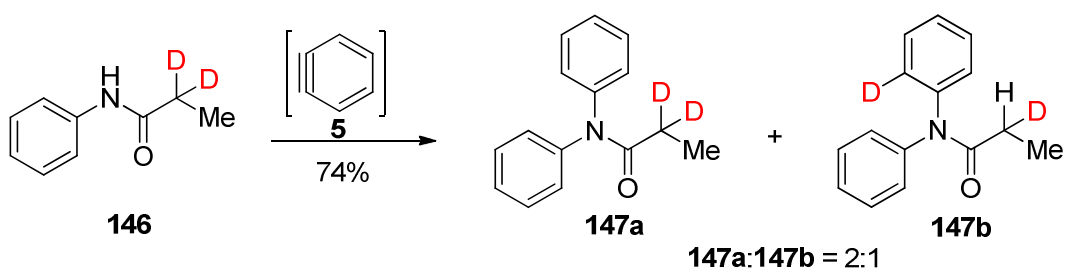


Figure 1.15. ^1H NMR comparison of non-deuterated and deuterated products.

1.4.6.3 Study C: Identification of the 1,5-hydrogen abstraction

quenching pathway



Scheme 1.44. Intramolecular 1,5-hydrogen abstraction quenching pathway.

To a solution of di-deuterated *N*-phenylpropionamide **146** (0.250 mmol) and TBAT (0.500 mmol) in toluene (3 mL) was added the benzyne precursor **9** (0.375 mmol). The reaction was heated at 50 °C for 16 h and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel (dry loading) to afford in a 74% isolated yield a mixture of inseparable di- and mono-deuterated *N,N*-diphenylpropionamide products in the ratio 2 : 1 based on ^1H NMR. ^2H NMR verified the deuterium shift onto the aromatic ring (Figure 1.16 and 1.17).

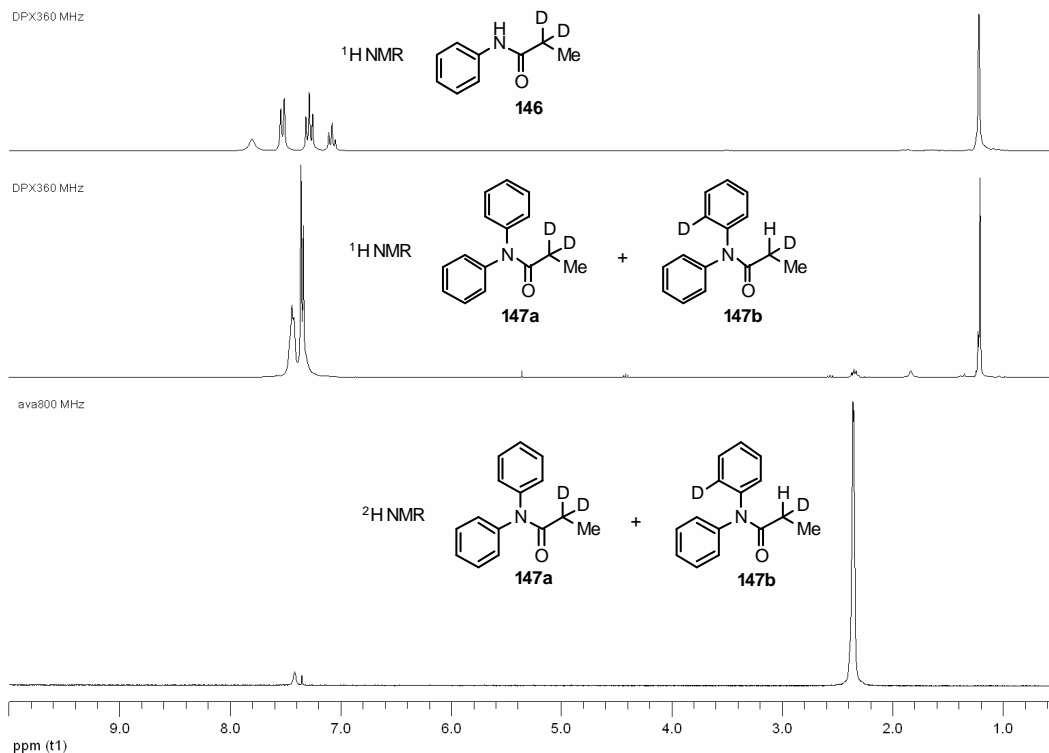


Figure 1.16. NMR identification of the 1,5-hydrogen shift.

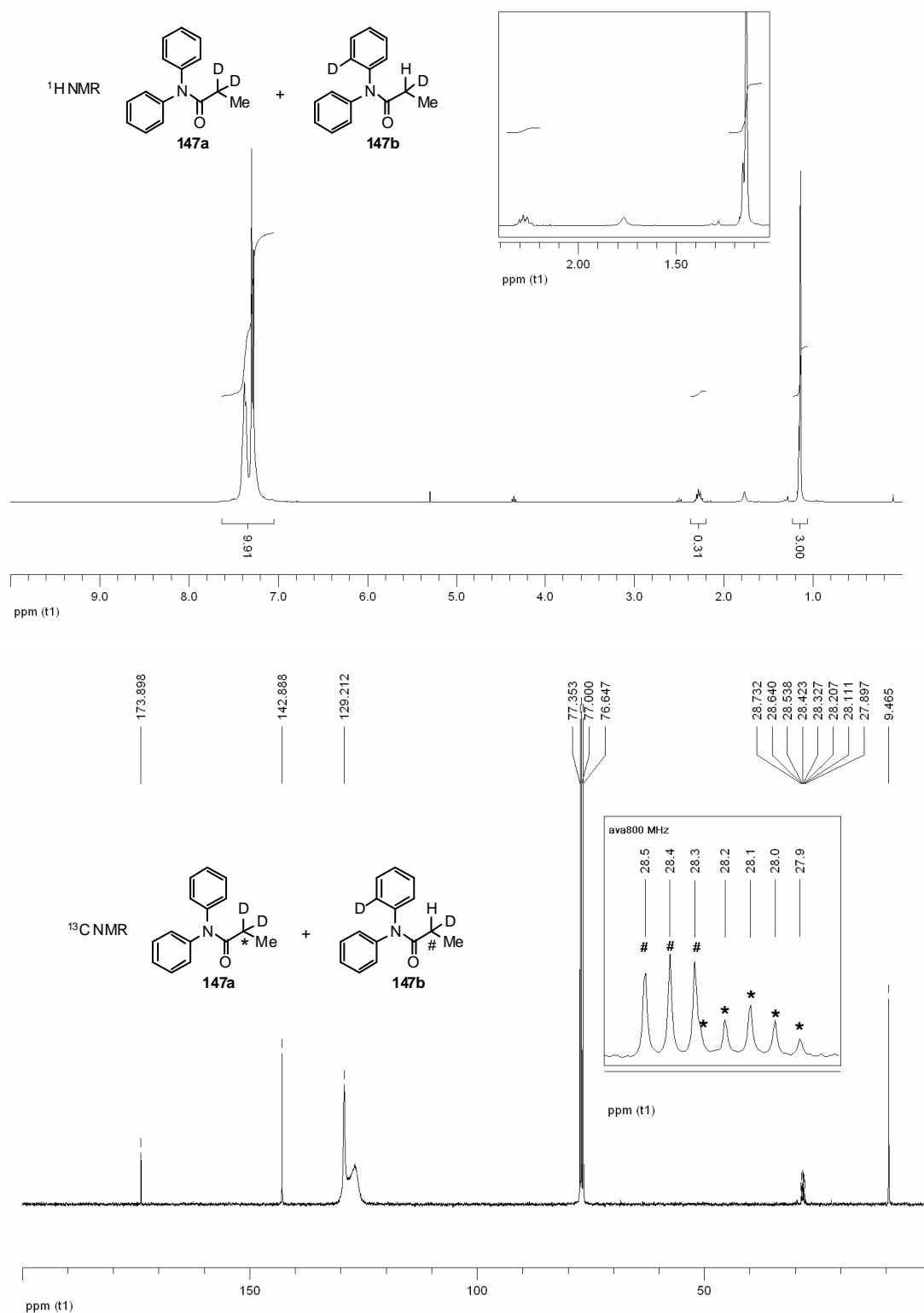


Figure 1.17. ^1H and ^{13}C NMR of the product mixture issue from the 1,5-hydrogen shift quenching pathway.

1.5 References for chapter 1

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Insertion of Benzene Rings into the Amide Bond: One-Step Synthesis of Acridines and Acridones from Aryl Amides

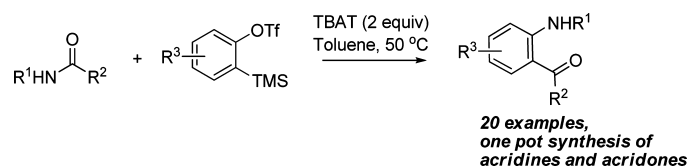
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Received November 5, 2009

ABSTRACT

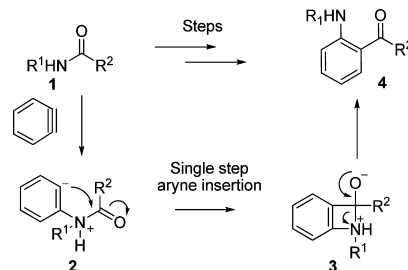


Insertion of benzene rings into the amide bond using the reactive intermediate benzyne is described. Aromatic amides undergo smooth insertion when treated with *O*-triflatophenyl silane benzyne precursors, producing versatile aminobenzophenone products in good to excellent yield. The process is entirely metal-free and has been exemplified on the synthesis of biologically active acridones and acridines.

The insertion of a benzene ring into amide bonds represents a powerful synthetic and topological transformation. The amide bond is split to form one new aryl C–N and one aryl C–C bond, forming aminobenzophenone products of fundamental importance in the synthesis of biologically active heterocycles such as benzodiazepines, quinolines, and acridones. While a number of multistep processes for the transformation can be envisaged,¹ a one-step, general method has yet to be developed. A possible solution to the problem is to employ the reactive intermediate benzyne in a σ -insertion reaction.^{2,3} The weakly nucleophilic amide nitrogen can attack the reactive aryne molecule, forming a zwitterion intermediate **2**, which can rearrange through the intermediacy

of a transient azetidinium ion **3** to produce the desired aminobenzophenone **4** (Scheme 1).

Scheme 1. Aryne Insertion into the Amide Bond



The amide insertion reaction has been demonstrated by Larock for one specific substrate class, activated trifluoroacetanilides ($R^2 = \text{CF}_3$).⁴ This valuable precedent, taken with

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(2) Review Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579–3581.

(3) Recent examples of aryne σ -insertion reactions: (a) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohl, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745–13754. (b) Yoshida, H.; Kishida, T.; Watanabe, M.; Ohshita, J. *Chem. Commun.* **2008**, *45*, 5963–5965. (c) Yoshida, H.; Morishita, T.; Ohshita, J. *Org. Lett.* **2008**, *10*, 3845–3847. (d) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699–5713. (e) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A. *J. Org. Chem.* **2008**, *73*, 5452–5457. (f) Beltran-Rodil, S.; Peña, D.; Guitián, E. *Synlett* **2007**, *8*, 1308–1310.

(4) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113. See also: Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247–3249.

our own interest in new aryne-based methods,⁵ encouraged us to develop an amide insertion reaction having broad utility.

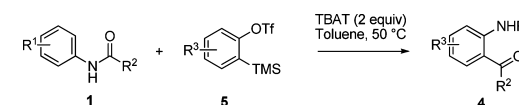
Using the versatile *O*-triflate silane **5a** ($R^3 = H$) as the aryne precursor,⁶ a survey of reaction solvents and fluoride sources established the viability of the reaction for *N*-pivaloylaniline **1a** (Table 1, entry 1). Stirring in toluene in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT) triggered a clean insertion at 50 °C, affording the *tert*-butylketone **4a** in 64% yield. Exploration of substrate scope⁷ showed the reaction to be general for a variety of aniline derivatives, enabling the preparation of diverse electron-poor and electron-rich aminobenzophenones in very good yield (entries 1–10). In each case the *N*-pivaloyl and *N*-phenyl derivatives were similarly efficient substrates. The aryne insertion reaction offers a new entry point to *tert*-butylarylketones that is operationally simple and does not require any metal reagents. Literature routes to this compound class are somewhat restricted and invariably use stoichiometric organometallics.⁸

Trifluoroacetanilides, previously investigated by Larock, were excellent substrates for the reaction, with the sterically hindered trifluoromethyl amide **1k** undergoing insertion in very high yield (entry 11). The reaction was also effective for *N*-heteroaryl substrates, with the furoyl derivative **1l** undergoing tandem furan Diels–Alder reaction and insertion in high yield when treated with an excess of benzyne (entry 12). The structure of the highly functionalized product **4l** was secured by X-ray crystallography.

We next examined substituted arynes in the reaction with *N*-phenylbenzamide (entries 13–15). The electron-rich methylenedioxy aryne **5b** underwent smooth insertion to produce the oxygenated benzophenone **4m** (entry 13). The unsymmetrical aryne precursors **5c** and **5d** produced insertion adducts as single regioisomers (entries 14 and 15), assigned as drawn on the basis of well-known selectivities in nucleophilic additions to unsymmetrical arynes.⁹ Finally, we examined the two imide derivatives **1m** and **1n** in the reaction, an important substrate class as it permits the preparation of protected amino ketones as versatile building blocks for heterocycle synthesis (Scheme 2). Insertion was selective for the amide over the carbamate linkage in both cases, providing the Boc and CBz-protected amines **4p** and **4q** in 70% and 75% yield, respectively.

We exemplified the power of the reaction as a rapid entry point to nitrogenated heteroaromatics by developing a divergent synthesis of acridones and acridines. These tricyclic aza-arenes are important targets in medicinal and materials chemistry having multifaceted biological (e.g., antimalarial,

Table 1. Amide Insertion

|  | | | | |
|--|--------------------------------|-----------|-----------|------------------------|
| entry | amide | aryne | product | yield (%) ^a |
| 1 | | 5a | | 64 |
| 2 | 1b $R^2 = Ph$ | | 4b | 81 |
| 3 | 1c $R^2 = m\text{-Tol}$ | | 4c | 88 |
| 4 | | 5a | | 71 |
| 5 | 1e $R^2 = Ph$ | | 4e | 85 |
| 6 | | 5a | | 61 |
| 7 | 1g $R^2 = Ph$ | | 4g | 76 |
| 8 | | 5a | | 69 |
| 9 | 1i $R^2 = Ph$ | | 4i | 81 |
| 10 | | 5a | | 65 |
| | 1j | | 4j | |
| 11 | | 5a | | 90 |
| | 1k | | 4k | |
| 12 ^b | | 5a | | 82 |
| | 1l | | 4l | |
| 13 | | | | 76 |
| | 1b | 5b | 4m | |
| 14 | | | | 65 |
| | 1b | 5c | 4n | |
| 15 | | | | 78 |
| | 1b | 5d | 4o | |

^a Isolated yields. Reaction conditions: amide (0.25 mmol), TBAT (0.50 mmol), and **5** (0.375 mmol) in toluene (3 mL); 50 °C for 16 h. ^b 2.8 equiv of **5a** added.

(5) (a) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199–5202. (b) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589–5592. (c) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426–7427.

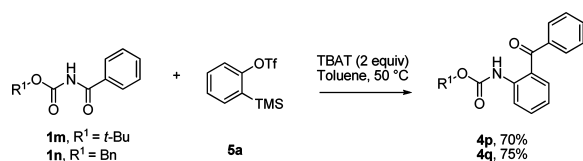
(6) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.

(7) See Supporting Information.

(8) (a) Díaz-Valenzuela, M. B.; Phillips, S. D.; France, M. B.; Gunn, M. E.; Clarke, M. L. *Chem.–Eur. J.* **2009**, *15*, 1227–1232. (b) Koreeda, T.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 7238–7239.

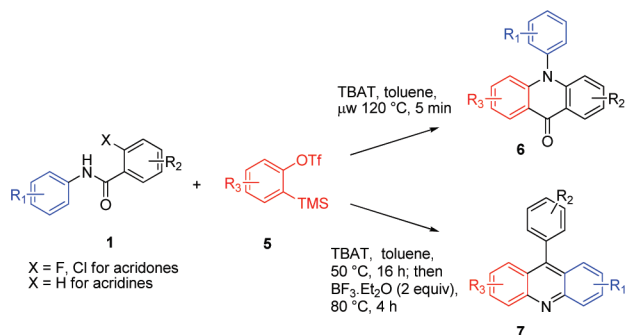
(9) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215–291.

Scheme 2. Imide Insertion



anticancer), optical, and redox properties.¹⁰ Acridones were accessed from readily available *o*-halobenzamides through initial aryne σ -insertion, followed by an in situ S_NAr reaction (Scheme 3).

Scheme 3. Divergent Synthesis of Acridones and Acridines



We developed a single-step method using just 5 min of microwave irradiation at 120 °C in the presence of TBAT (Table 2, entries 1–5). The compatibility of precursors **5** with microwave heating has recently been remarked upon and is testament to their superb versatility in aryne chemistry.¹¹ Yields of acridones were generally excellent; in the case of the 3-methyl aryne precursor **5d**, a 1:1 mixture of regioisomeric acridones was isolated, underlining the intermediacy of the reactive aryne intermediate in the reaction (entry 4).¹²

We could divert the insertion product to the acridine structure **7** through Lewis acid mediated intramolecular Friedel–Crafts acylation and dehydration. Again, the versatility of the aryne precursors enabled the development of a one-pot procedure: adding BF₃·OEt₂ to the reaction mixture following insertion and increasing the reaction temperature to 80 °C produced good yields of diverse acridine products (Table 2, entries 6–10). Each synthesis incorporates the aryne moiety into the heterocycle framework and can be directed toward the display of either *N*-aryl (acridones) or *C*-aryl (acridines) groups according to the cyclization conditions.

(10) Kelly, J. X.; Smilkstein, M. J.; Brun, R.; Wittlin, S.; Cooper, R. A.; Lane, K. D.; Janowsky, A.; Johnson, R. A.; Dodean, R. A.; Winter, R.; Hinrichs, D. J.; Riscoe, M. K. *Nature* **2009**, 459, 270–273.

(11) (a) Ankati, H.; Biehl, E. *Tetrahedron Lett.* **2009**, 50, 4677–4682. (b) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, 11, 1587–1590.

(12) For an alternative acridone synthesis involving aryne addition to aminobenzophenones, see: Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, 72, 583–588.

Table 2. Acridone and Acridine Synthesis

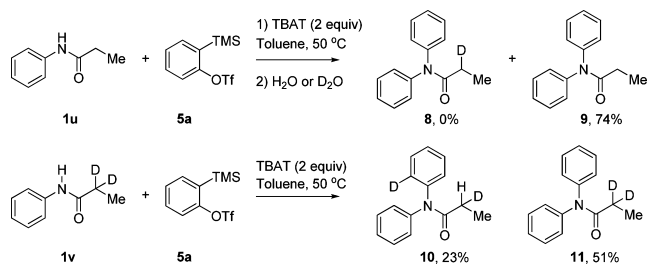
| entry | amide | aryne | product | yield (%) ^a |
|-------|-------|-------|---------|------------------------|
| 1 | | | | 92 |
| 2 | | | | 62 |
| 3 | | | | 89 |
| 4 | | | | 85 ^b |
| 5 | | | | 88 |
| 6 | | | | 72 |
| 7 | | | | 78 |
| 8 | | | | 67 ^b |
| 9 | | | | 74 |
| 10 | | | | 62 |

^a Isolated yields. Reaction conditions: for acridones, amide (0.25 mmol), TBAT (0.75 mmol), and **5** (0.75 mmol) in toluene (3 mL); 120 °C, 5 min; for acridines, amide (0.25 mmol), TBAT (0.50 mmol), and **5** (0.425 mmol) in toluene (3 mL); 50 °C, 16 h, then BF₃·Et₂O (0.50 mmol), 80 °C, 4 h. ^b 1:1 mixture of regioisomers.

Insertion substrates containing hydrogens adjacent to the amide bond generally underwent preferable *N*-phenylation under the reaction conditions. Given that the first step of the σ -insertion reaction is proceeding, the failure to rearrange may be due to an intramolecular proton abstraction in the zwitterion **2** quenching the reaction (Scheme 1).¹³ To gain

insight into the mechanism, we carried out deuterium labeling studies using *N*-phenylpropionamide **1u** (Scheme 4). Stirring

Scheme 4. Deuterium Labelling Studies



under the standard conditions of TBAT for 16 h, followed by aqueous workup, produced the *N,N*-diphenyl compound **9** in high yield. Repeating the reaction with a D_2O quench produced the same result, as did running the reaction in d_6 -benzene as reaction solvent. Repeating the reaction using the doubly deuterated derivative **1v** produced an identical yield of the *N,N*-diphenyl compound, as a ca. 1: 2 mixture of **10** and **11**.

(13) A similar intramolecular quenching mechanism has been identified in the aza-Fries rearrangement of iodoarylamides when treated with butyl lithium; see ref 1b.

The incorporation of deuterium in the aryl ring of **10** implicates 1,5-hydrogen abstraction as a minority quenching mechanism for alkyl-substituted amide substrates. The major quenching pathway is likely from transfer of the amide proton to the phenyl anion, confirmed by reacting the *N*-D derivative of **1u** with benzyne and observing deuterium incorporation into the aryl ring of the product.⁷

In conclusion, we have developed an aryne σ -insertion reaction for the ubiquitous aryl amide and imide functional groups. The process is high-yielding and operationally simple and uses no metal reagents. The process has been applied to the one-pot synthesis of acridones and acridines; further applications to biologically relevant targets are underway in our group.

Acknowledgment. We thank the University of Edinburgh for the award of a studentship to D.G.P. and the EPSRC mass spectrometry service at Swansea. Dr. Fraser White is thanked for X-ray crystallography.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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CHAPTER 2

Medium-ring synthesis by oxidative C-H coupling

2.1 General introduction on palladium catalysis

2.1.1 Traditional cross-coupling reaction

Very recently the 2010 Nobel Prize for chemistry has been awarded to the well-known trio of organic chemists, Richard Heck, Ei-ichi Negishi and Akira Suzuki, for creating, in the judges words, “great art in a test tube”. The three recipients were given science’s most prestigious award for their tremendous contribution to palladium catalysed Carbon – Carbon bond formation by cross-coupling reaction. Indeed, they revolutionised the way of connecting aromatic carbon atoms together and developed synthetic transformations for making bi(hetero)aryl compounds under mild reaction conditions and with high degrees of selectivity.

Such cross-coupling reactions are now carried out routinely in research laboratories and industrial processes to synthesise biaryl building blocks of complex molecules. However, despite the structural simplicity of biaryl scaffolds and their large abundance in medicinal agents, electronic materials and natural products; the preparation of biaryl molecules still appears to be challenging (Figure 2.1).^{1,2} Thus, for more than hundred years, the preparative complexity of the (hetero)arene – (hetero)arene linkage captivated synthetic chemists.³

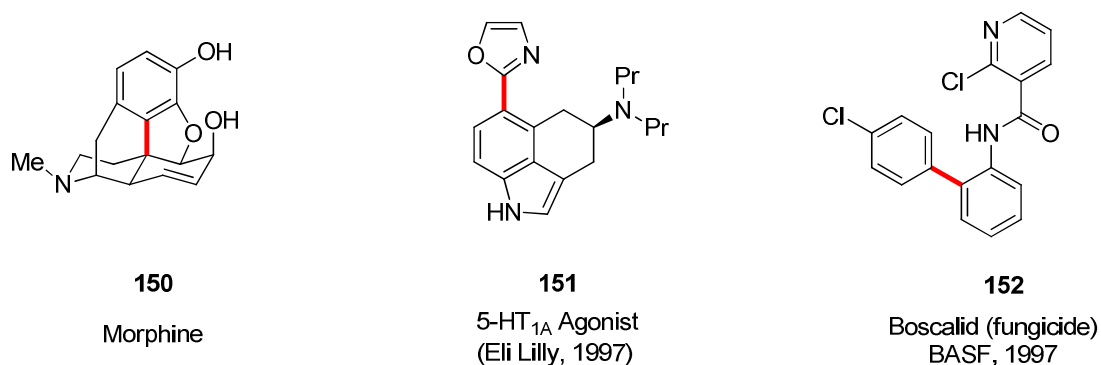
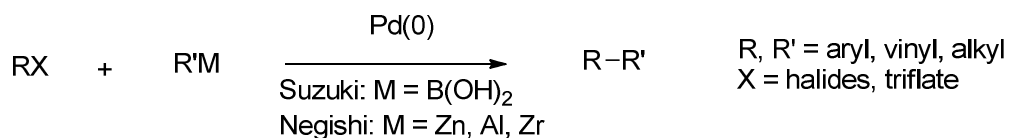


Figure 2.1. Examples of biologically active molecules made *via* Heck, Negishi and Suzuki cross-coupling reaction.

Although the Suzuki reaction and similar palladium catalysed cross-coupling reactions are still the methods of choice for the generation of biaryl cores, a specific pre-functionalisation of the two coupling partners is still required for them to react. Indeed, these cross-coupling processes require the independent preparation of an

electrophilic species (R-X, quite often X = halides or triflate) and a nucleophilic species (R'-M, quite often is an organometallic or organoboron compound) before reaction (Scheme 2.1).

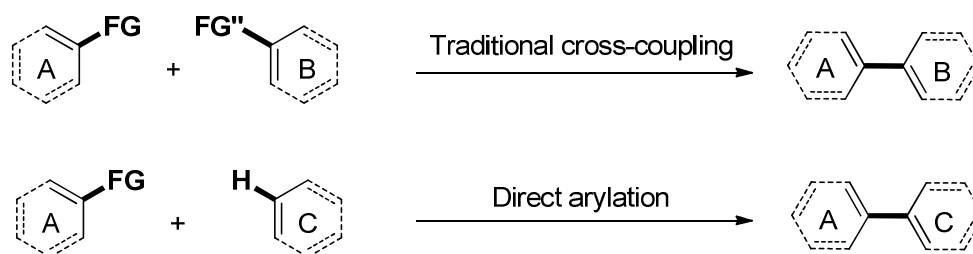


Scheme 2.1. General Suzuki and Negishi cross-coupling reaction.

The incorporation of these functional groups can sometimes require multiple synthetic steps which often increase the cost associated with undesired reaction by-products, waste disposal from reagents, solvents and purification residues. The fact that these traditional cross-coupling processes are not very atom economic has pushed synthetic chemists to develop new alternative cross-coupling reactions. Therefore, chemists have then replaced one of the two pre-activated partners for cross-coupling with a simple inactivated (hetero)arene and performed what has been commonly called transition-metal catalysed direct arylation reactions.^{4,5}

2.1.2 Direct Arylation

An attractive alternative to classic cross-coupling reaction is to treat the aryl Carbon – Hydrogen bond (C-H) as a functional group, in analogy to a carbon - metal or carbon – (pseudo)halogen bond. In direct arylation, Ar-H is directly used as the nucleophile and no aryl metal reagent (Ar-M) is needed anymore. Thus, this allows synthetic chemists to directly assemble benzenoid motifs from simple arenes with aryl (pseudo)halides (Scheme 2.2).

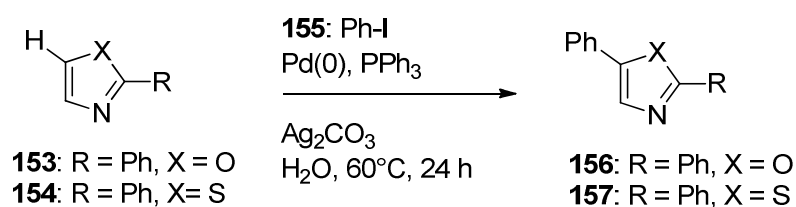


Scheme 2.2. Traditional cross-coupling and direct arylation reactions.

This process has the advantage of being less hazardous for users and the environment since the use of equimolar amount of toxic metals such as tin is eliminated. In addition, the atom economy of the reaction is increased immensely as the metal, generally of high molecular weight, is replaced by the smallest possible atom, hydrogen.

Over the past decade, the field of direct arylation has been extensively reviewed by pioneers in the field of transition-metal catalysed cross-coupling reactions. Indeed, Lautens and Alberico, Fagnou, Sanford and Dick, and more recently Ackermann, McGlacken and Bateman have highlighted and discussed the advances made in the field.⁴⁻⁸ This collection of recent reports was completed by Sames and Godula and their review published in *Science* on “C–H bond functionalization in complex organic synthesis”.⁹ An additional review by Satoh and Miura discussed the “catalytic direct arylation of heteroaromatic compounds”¹⁰ while Larrosa and Boorman recently reviewed “recent advances in C-2 regioselective direct arylation of indoles”¹¹

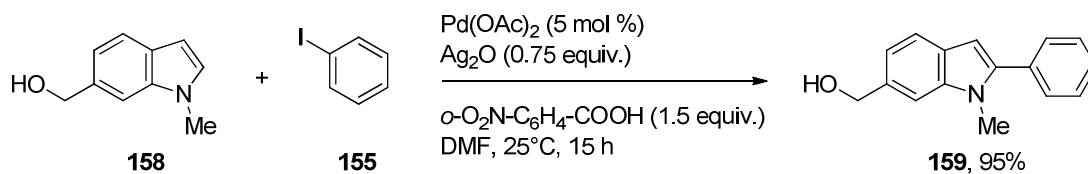
Since 2006, the Greaney group also played a key role in the area of direct arylation. In the hunt for the discovery of greener arylation processes, Greaney and co-workers have successfully developed a direct arylation system of azoles that works “on water” (Scheme 2.3).¹²⁻¹⁴



Scheme 2.3. “On water” direct arylation of oxazoles and thiazoles.^{12,13}

These transformations proceed under mild conditions of temperature and require water as unique “solvent”. This permits the efficient arylation of azoles displaying diverse functionalities of relevance to medicinal, materials, and natural products chemistry.

Following the same idea of developing greener direct arylation processes, Larrosa and co-workers have reported an efficient room temperature and phosphine ligand free methodology for the C-2 direct arylation of indoles (Scheme 2.4)



Scheme 2.4. Room temperature and phosphine free C-2 direct arylation of indoles.

Despite the immense advances made regarding the synthetic efficiency and the environmental impact of transition-metal catalysed cross-coupling reactions, the direct arylation approach is still not the most atom economic. Indeed, as mentioned previously, the coupling of aromatic molecules by direct arylation requires the pre-synthesis of an (pseudo)halide as the electrophilic partner. This (pseudo)halide is rarely directly available in nature and has to be synthesised separately, multiplying the cost and the steps of the synthetic process.

In theory, the most direct approach for the synthesis of aryl C-C linkage is through double C-H bond activation. The oxidative formation of C-C bond with a net loss of two protons represents the optimum level of arylation reactions. Over the past 10 years, synthetic chemists have focused their research on oxidative coupling of benzene with unactivated or activated (hetero)arenes to synthesise biaryl molecules. So far, important progresses have already been made in terms of substrate scope and reaction conditions understanding and more can certainly be anticipated. Considering the early stage of the area, our group recently decided to contribute to the development of novel and challenging oxidative coupling transformations.

Considering the Greaney group's background on direct arylation of heterocycles, I have focused my research on the development of new catalytic oxidative coupling reactions of heteroaromatic compounds.

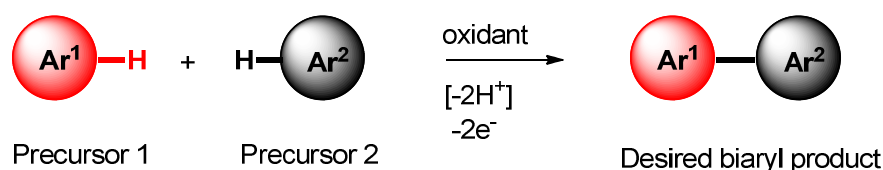
In this chapter, I will firstly discuss the background of oxidative arene-arene coupling, then I will describe about the research I carried out, and finally, based on the results obtained, I will propose some directions for future work.

2.2 Introduction on oxidative C-H coupling

2.2.1 General considerations

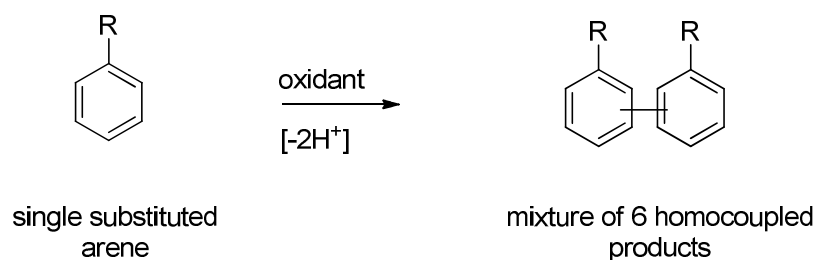
Natural resources such as natural gas and petroleum represent the largest and cheapest feedstock of aromatic hydrocarbons (Ar-H) on earth.¹⁵ However, given the strength of the C-H bond, the direct coupling of two unactivated benzene type molecules to form a biaryl building blocks is thermodynamically unfavoured. Indeed, Dasgupta and Maiti have shown that benzene can react with itself at high temperature to produce biphenyl but this thermal dimerization is thermodynamically disfavoured by 13.8 kJ/mol.¹⁶

Transition-metal catalysed C-H bond activation and functionalisation of unactivated arenes represents the most straightforward route for the synthesis of valuable compounds.^{15,17,18} Indeed, catalytic oxidative coupling reactions do not require any pre-functionalisation of the arenes to generate aromatic halides as electrophilic coupling partner and aryl metals as nucleophilic coupling partners (Scheme 2.5).



Scheme 2.5. Oxidative coupling reaction of unsubstituted arenes

Although the homocoupling reaction of benzene does not present any problem of selectivity and regioselectivity, the coupling between two substituted and/or different arenes faces many challenges. Indeed, in the case of the oxidative coupling of a substituted and/or unsymmetrical arene, due to the ubiquity and large number of C-H bonds available for activation, the final reaction mixture would result in a terrible mixture of homocoupled regioisomeric reaction products (Scheme 2.6). Additionally, if we take the example of the coupling between two different molecules the reaction conditions must be carefully chosen to favour the heterocoupling product and to avoid the formation of any homocoupling product.



Scheme 2.6. Dimerization of a simple mono-substituted arene

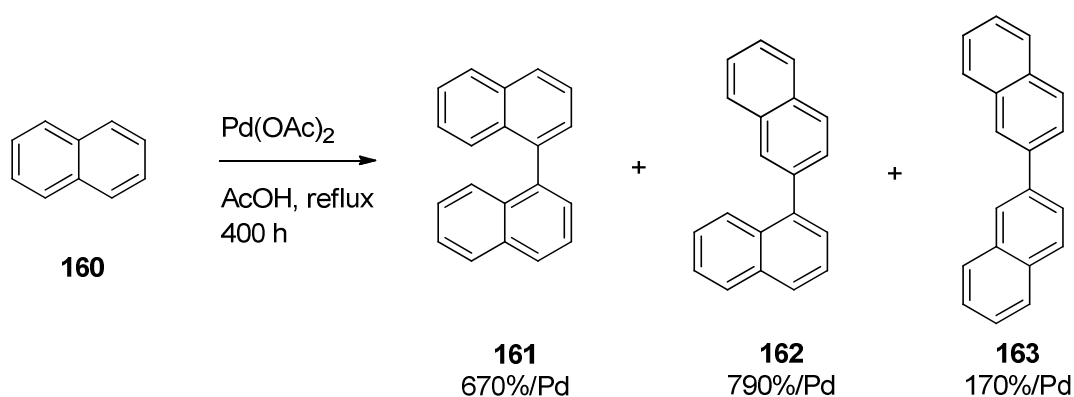
The selectivity of the C-C bond formed would be determined by the steric and electronic preferences of the two partners. In the absence of activating groups, the combination of these two factors, steric and electronic, could result in the formation of disastrous mixtures of products.

Due to the infancy of the field of transition-metal catalysed oxidative coupling reaction, only few reviews have been published so far. I would like to quickly go through the chemistry already discussed by Kakiuchi and Kochi,¹⁹ Jin-Quan Yu *et al.*,²⁰ McGlacken and Bateman,⁸ and recently presented by Ashenhurst²¹ and Lei *et al.*²² and I would also like to describe in more detail the chemistry recently published.

2.2.2 Early age of oxidative coupling

2.2.2.1 Oxidative homocoupling of arenes

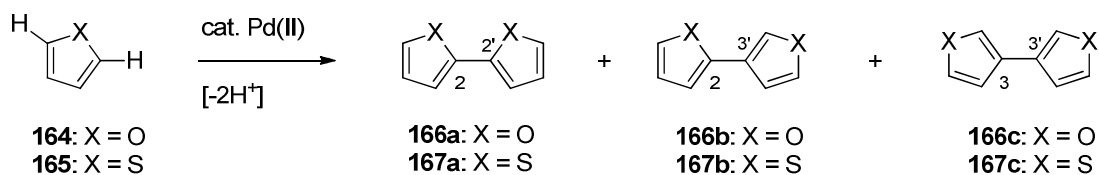
The formation of biphenyl by dimerization of benzene was the reaction targeted by pioneers in the field during the mid 60's. Many stoichiometric and few palladium catalysed reactions have been reported at that time. Indeed, Van Helden and Verberg used stoichiometric amount of palladium chloride with sodium acetate to achieve the transformation,²³ whereas Itatani and Yoshimoto used catalytic Pd(EDTA) under high pressure of oxygen to accomplish the same reaction.²⁴⁻²⁶ Subsequently in 1973, other groups reported the combination of catalytic palladium II species with other metals such as mercury²⁷ and thallium²⁸ for the homocoupling of benzene and substituted benzene. The same year, the dimerization reaction of naphthalene using palladium acetate in refluxing acetic acid for 400 hours was also reported.²⁹ However, this oxidative transformation occurred with low selectivity and a wide range of products was obtained during the reaction (Scheme 2.7).



Scheme 2.7. Oxidative coupling of naphthalene carried out by Eberson and Gomez-Gonzalez in 1973.²⁹

2.2.2.2 Oxidative homocoupling of heteroarenes

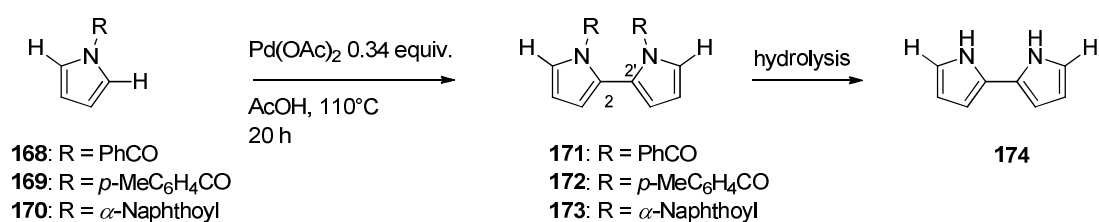
Oxidative dimerization of simple aromatic heterocycles has also been reported from the mid 70's. Indeed, Kozhevnikov *et al.* reported the oxidative coupling of 5-membered heterocycles such as furans and thiophenes using palladium (II) in aqueous or organic solutions (Scheme 2.8).^{30,31}



Scheme 2.8. Catalytic oxidative homocoupling of furans and thiophenes.

As with the previous case, homocoupling of substituted benzenes, the homocoupling of furans and thiophenes proved to be non-selective. Overall, when using furans or thiophenes, a mixture of 2, 2'- and 2, 3'-isomers, as well as traces of the 3, 3'-isomer were obtained. 2,2'-isomers **166a** and **167a** were the predominate species formed in accordance with the kinetically preferable direction of electrophilic substitution in 5-membered heterocycles. Other heterocycles such as pyrroles were also used, but very poor yields could be obtained.³⁰

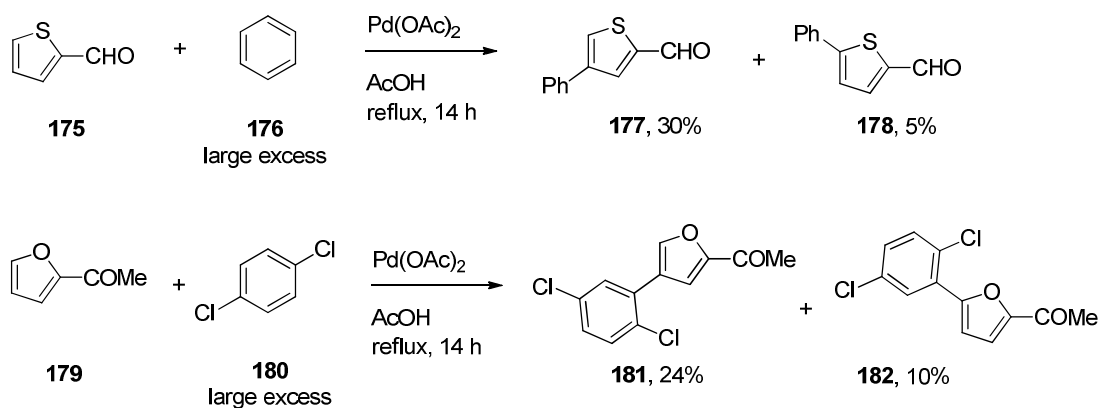
A couple of years later, Itahara gave his full attention to the synthesis of polypyrroles by catalytic oxidative dimerization of pyrroles derivatives.³² 1-Benzoylpyrroles were successfully homocoupled in the presence of catalytic palladium acetate in acetic acid at 110 °C and 2,2'-bipyrroles **174** could be isolated in about 45 to 55 % yield (Scheme 2.09). In another paper, the author suggested that the exclusive selectivity of the reaction was due to the intramolecular directing effect of the benzoyl group. This represented one of the first example of the use of directing group in oxidative coupling to control the selectivity of the reaction.³³



Scheme 2.9. Catalytic oxidative homocoupling of 1-benzoylpyrroles.

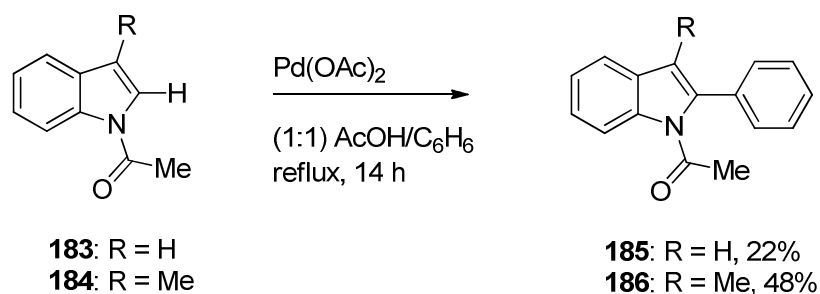
2.2.2.3 Oxidative heterocoupling of arene and heteroarene

Although the homocoupling of (hetero)arenes was challenging to achieve from a synthetic point of view, the transformation was limited to a small range of substrates and to a small diversity of products. Heterocoupling between arenes and heteroarenes represented the ideal way to increase diversity in the reaction. In 1985, Itahara *et al.* described the first oxidative cross-coupling reaction between aromatic heterocycles and arenes.³³ The authors found that treatment of 2-formyl and 2-acetyl furan and thiophene derivatives with arenes and palladium (II) acetate gave the corresponding 4-aryl-substituted furan **181** and thiophene **177** together with small amounts of the 5-aryl-substituted furan **182** and thiophene **178**. A selection of transformations performed in the related paper is highlighted in Scheme 2.10.



Scheme 2.10. Oxidative coupling of selected thiophene and furan derivatives with arenes.

Subsequently, they also carried out the first direct C-H activation and C-arylation of pyrroles and indoles with unactivated arenes. Indeed, treatment of 1-acetylindole **183** or 1-acetyl-3-methylindole **184** with palladium acetate in acetic acid and benzene gave respectively 1-acetyl-2-phenylindole **185** and 1-acetyl-2-phenyl-3-methylindole **186** (Scheme 2.11).



Scheme 2.11. First palladium catalysed oxidative coupling of indole with benzene.

This work represented a large step forward in the area of palladium catalysed oxidative coupling arylation as it permitted to couple two different unactivated substrates together. However, it is also important to point out the drawbacks of this transformation which are the low selectivity and the poor yields of the reaction.

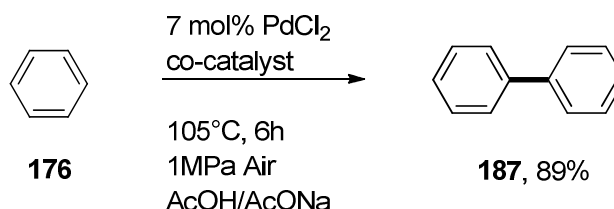
The novelty and the drawbacks of the reaction have inspired and pushed many synthetic chemists to improve and develop new catalytic oxidative coupling reactions.

The section below will be focused on modern palladium catalysed oxidative transformation and papers will be organised according to their general theme.

2.2.3 Recent advance in C-H activation

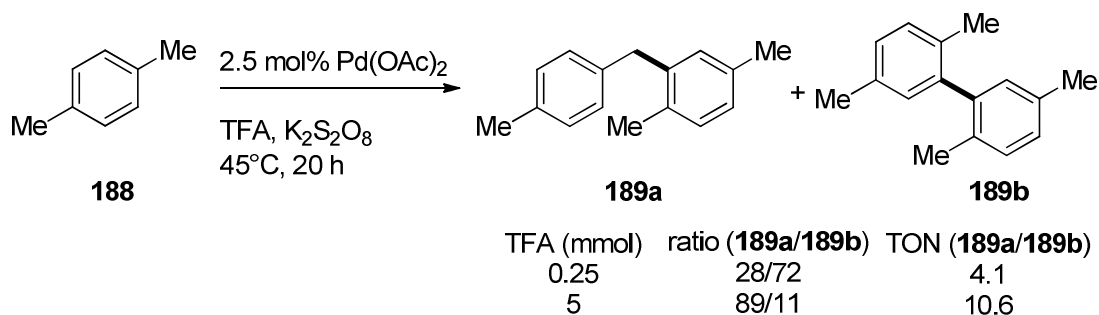
2.2.3.1 Intermolecular oxidative coupling

In 2001, Sasson *et al.* reported the homocoupling of benzenes to biphenyls using air or oxygen, palladium(II) chloride as the catalyst and a co-catalyst made of zirconium(IV), cobalt(II), and manganese(II) acetates.³⁴ Although the exact role of the co-catalyst is still unclear, the author suggested that the oxygen-binding catalysts present in the reaction mixture would increase the oxygen content in solution and therefore decrease the rate of decomposition of palladium to palladium black. Biphenyl could be isolated in 89% yield based on benzene (Scheme 13). However, despite the high conversions obtained for substituted benzenes, the reaction appeared to be poorly selective.



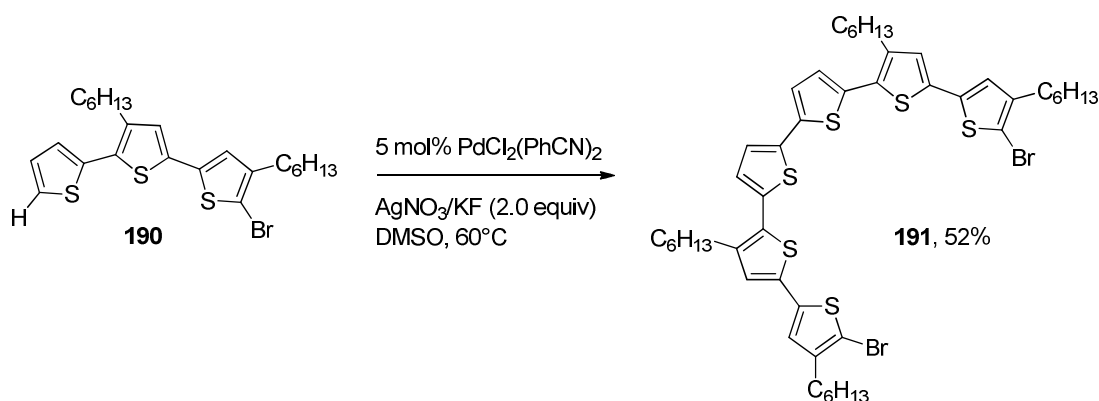
Scheme 2.12. Palladium catalysed oxidative homocoupling of benzene.

Later in 2006, Lu and co-workers worked on the regioselective C-H bond activation of toluene, xylenes and mesitylene. The reaction was catalysed by Pd(OAc)₂ in TFA and potassium persulfate (K₂S₂O₈) was used as oxidant.³⁵ The amount of TFA used in the reaction was a critical parameter and controlled the ratio of biaryl **189b** or diarylmethane **189a** formation (Scheme 2.13). Indeed, either biaryl- or diarylmethane can be formed as a major product by tuning the concentration of TFA.



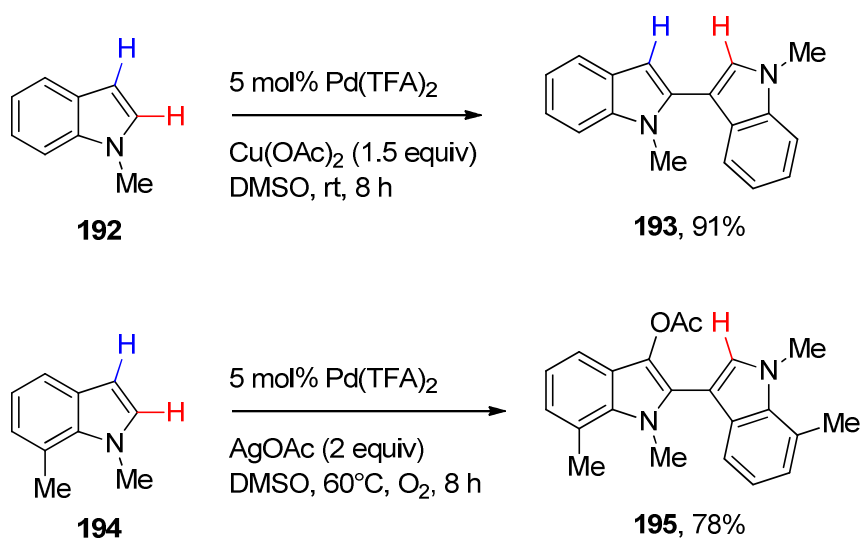
Scheme 2. 13. Palladium catalysed oxidative homocoupling of *p*-xylene.³⁵

Heterocycles also show homocoupling. In the last few years, well defined bithiophene structures and oligothiophenes were prepared by C–H homocoupling (Scheme 2.14).^{36,37} Low amounts of palladium catalyst [3 to 5 mol% of $\text{PdCl}_2(\text{PhCN})_2$] and stoichiometric amount of silver(I) fluoride or AgNO_3/KF in DMSO were required for the reaction to occur. Mori and co-workers focused their methodology on a very specific type of thiophene derivative, bromothiophene **190** shown in scheme 2.14. It is also noticeable that in these reactions the C–Br bond remained intact allowing further functionalisation.



Scheme 2.14. Palladium catalysed oxidative homocoupling of oligothiophenes.

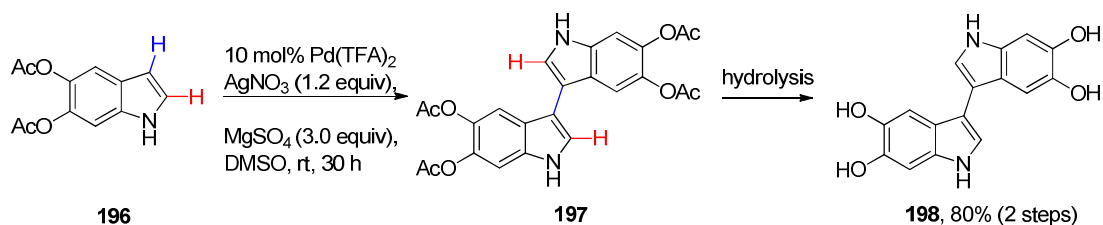
Dimerization of indoles recently attracted chemist's attention, and in 2010, two publications were published. Zhang and co-workers focused their effort on the unsymmetrical dimerization of indoles, creating a new carbon–carbon bond between the position C(2) and C(3) of indoles.³⁸ 2,3'-biindolyls were formed in high yield under mild reaction conditions and the chemistry has since been expanded to the one-pot synthesis of C3-acetoxylated biindolyls using silver acetate as oxidant (Scheme 2.15).



Scheme 2.15. Palladium catalysed unsymmetrical oxidative dimerization of indoles.

By slightly changing the reaction conditions, Shi's group managed to symmetrically homocouple indoles to afford 3,3'-linked biindolyl scaffolds **197**.³⁹

They exemplified the power of their methodology for the rapid synthesis of a phenolic antioxidant found in beetroot (Scheme 2.16).

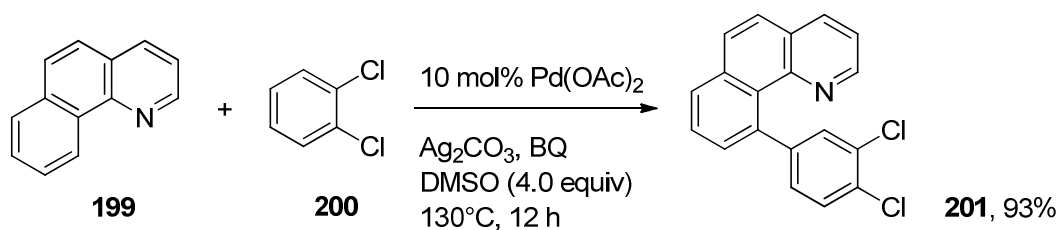


Scheme 2.16. Palladium catalysed symmetrical oxidative dimerization of indoles.

As mentioned previously, one of the main challenges which synthetic chemists are facing is the control of regioselectivity in the oxidative coupling reaction. One method by which the regioselectivity of arene arylation can be controlled is through the use of directing groups. Commonly used directing groups bear a lone pair of electrons that can coordinate to transition-metal catalysts to direct the activation of the C-H bond *via* a five- or six-membered metallacycle. A few groups have already

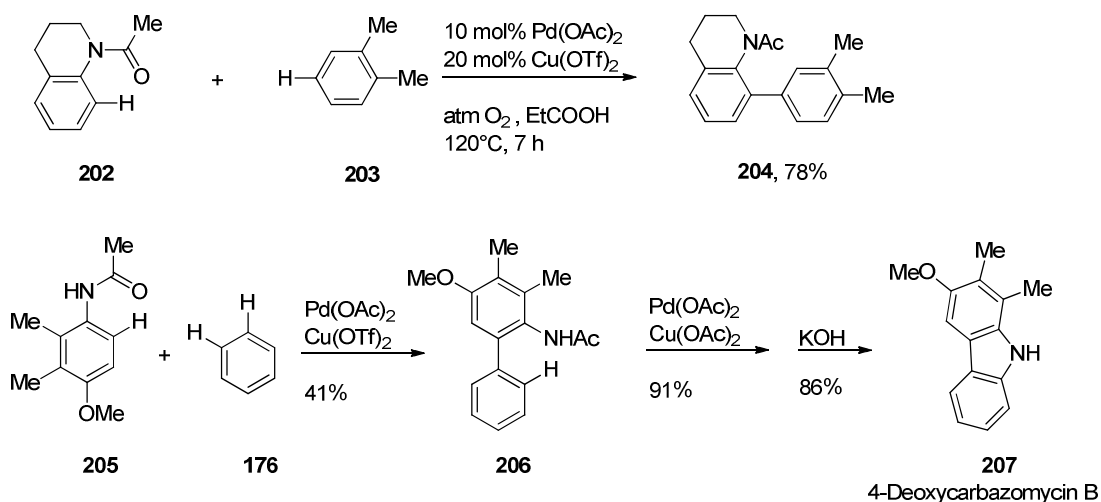
used this technique to activate and functionalise specific C-H bonds. Their work is highlighted below.

In 2007, Sanford and co-workers reported the catalytic and highly regioselective cross-coupling of benzoquinoline **199**.⁴⁰ The reaction of benzoquinoline **199** with 1,2-dichlorobenzene **200** in the presence of palladium(II) acetate as the catalyst, stoichiometric amount of silver carbonate and benzoquinone (BQ) as the oxidant afforded **201** in 93% yield (Scheme 2.17). The authors suggested that the nitrogen atom could coordinate to the palladium catalyst and direct the arylation.



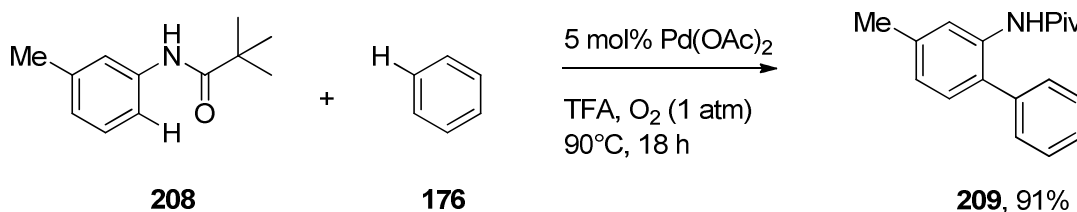
Scheme 2.17. Palladium catalysed oxidative coupling of benzoquinoline with arene.

In 2008, Shi and co-workers reported the development of a more environmental friendly synthesis of biaryls and biologically active compounds (Scheme 2.18).⁴¹ Indeed, the chemistry needed catalytic palladium (II), catalytic copper (II) triflate as oxidant and oxygen as co-oxidant to achieve the transformation. Acetamino directing groups, together with the steric hindrance of the aryl coupling partner were used to achieve regioselectivity in the arylated amides. They also exemplified the power of their methodology with the synthesis of carbazoles.



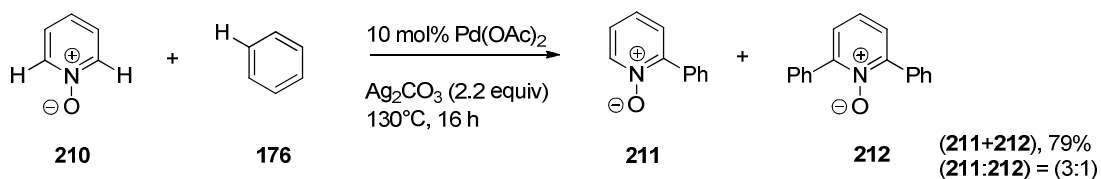
Scheme 2.18. Palladium catalysed oxidative coupling with acetamino directing-group containing arenes.

Almost at the same time Buchwald *et al.* revealed the *ortho*-arylation of pivanilide derivatives with benzenes.⁴² The reaction was catalysed by palladium (II) acetate in TFA with oxygen acting as the oxidant. Similarly to Sanford's work on the arylation of benzoquinoline,⁴⁰ 10–20 % DMSO were also required to slow down the formation of palladium black in the reaction (Scheme 2.19).



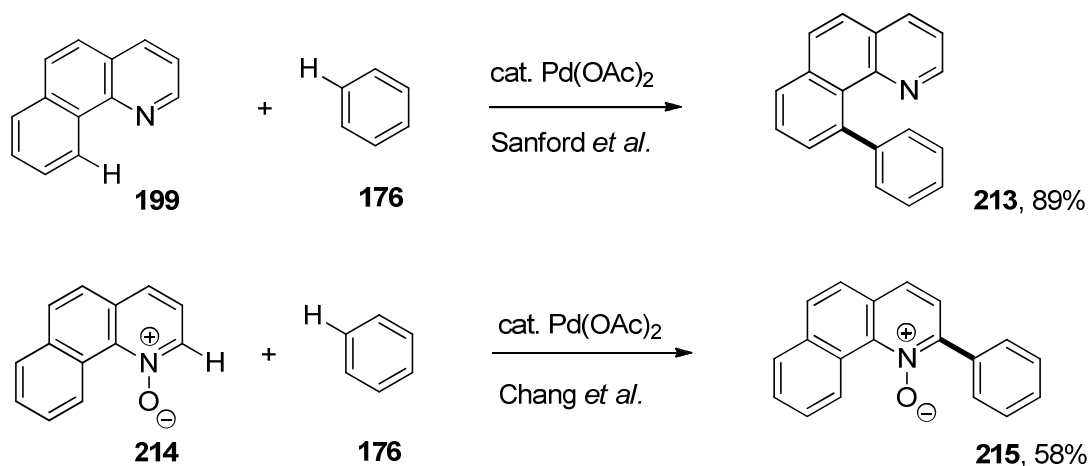
Scheme 2.19. Palladium catalysed oxidative coupling of pivanilides with benzenes.

Pyridine *N*-oxides were also good substrates for selective phenylation. The coupling between pyridine *N*-oxides and benzenes was selective for the less hindered *ortho*-position but the authors could not avoid the formation of both *mono*- and *bis*-orthoarylated products.⁴³ The reaction required catalytic amounts of palladium acetate, excess silver carbonate (2.2 equiv.) and a large excess of the arenes (40 equiv.) at 130 °C (Scheme 2.20). Oxidative coupling of pyridine *N*-oxides with arenes represents an attractive alternative way for the direct arylation of pyridine which still remains a challenge to work with.



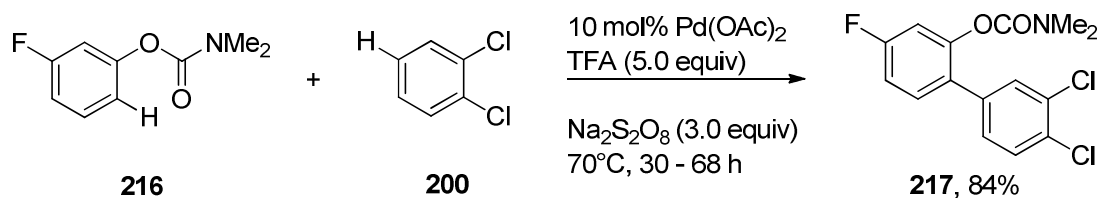
Scheme 2.20. Palladium catalysed oxidative coupling of pyridine *N*-oxides with benzenes.

Surprisingly, benzoquinoline *N*-oxides were arylated selectively at the *ortho*-position C(2) in good yield.⁴³ This is noteworthy because previous work performed by Sanford and co-workers on oxidative arylation of benzoquinolines has shown to proceed selectively at the C(10) position.⁴⁰ Both complementary routes are highlighted in Scheme 2.21.



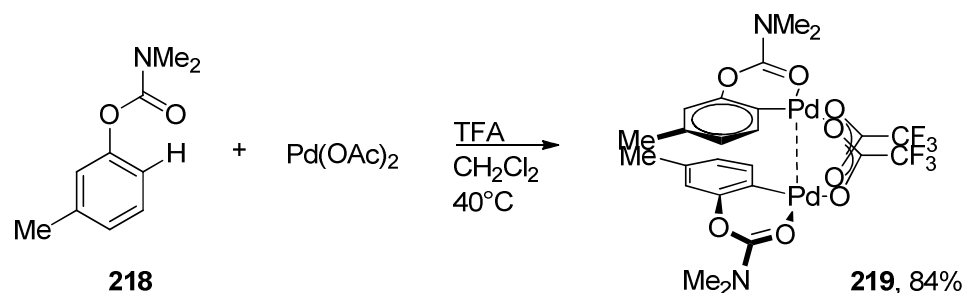
Scheme 2.21. Regioselective arylation of benzoquinolines⁴⁰ and benzoquinoline *N*-oxides.⁴³

In a very recent report published in January 2010, Dong and co-workers used the ability of *O*-carbamate directing-groups to selectively arylate phenol derivatives.⁴⁴ The authors were able to tune the reaction for *mono*- or *bis*-orthoarylation of *O*-phenylcarbamates with simple arenes. The reaction needed a specific combination of TFA and sodium persulfate to occur effectively (Scheme 2.22).



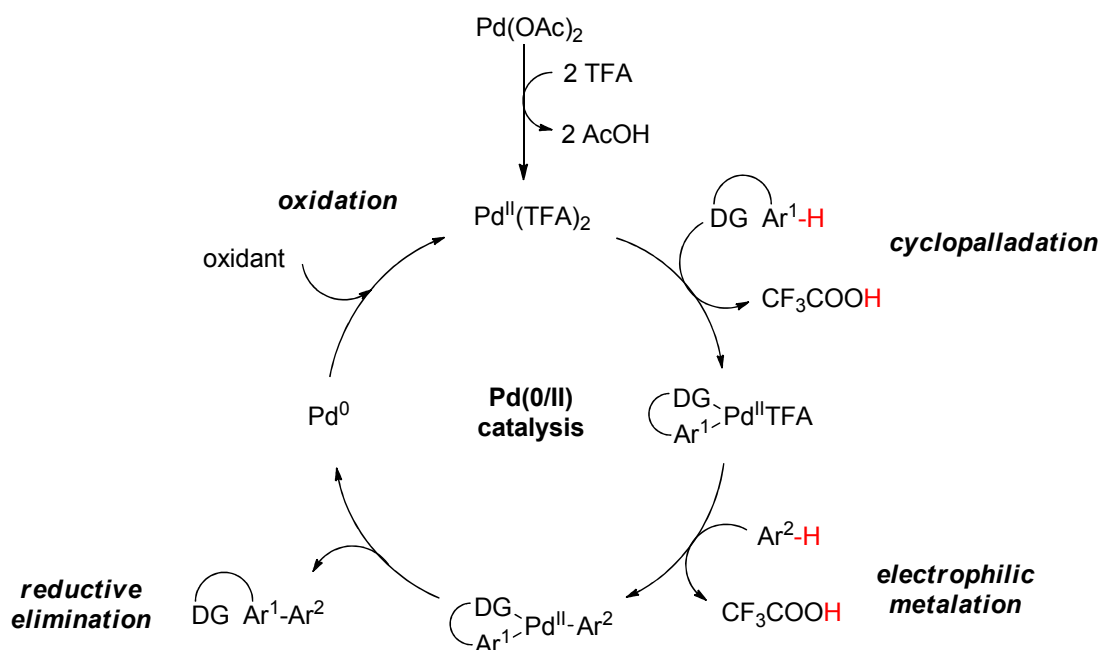
Scheme 2.22. Palladium catalyzed oxidative coupling of *O*-phenylcarbamates with arenes.

Palladacycle **219** showing the directing effect of the carbamate functional group has been synthesised by mixing *m*-tolyl dimethylcarbamate **218** with Pd(OAc)₂ in TFA and characterised by X-ray crystallography (Scheme 2.23).



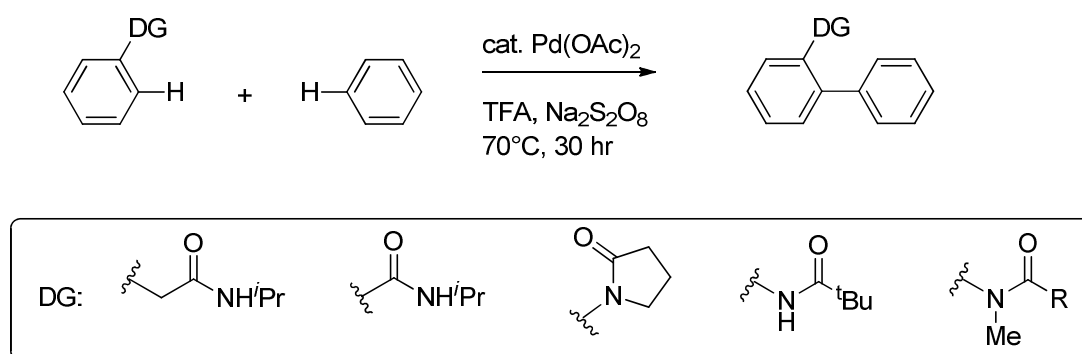
Scheme 2.23. Preparation of dimeric palladium complex **219**.

Getting the dimeric palladacycle **219** was crucial to get some insight into the mechanism of the reaction. The authors proposed that the oxidative coupling occurred *via* a Pd(0/II) catalytic cycle. Firstly, the mechanism involved a C-H bond activation by carbamate-assisted cyclopalladation, followed by C-H bond functionalisation by electrophilic aromatic substitution (S_EAr), then reductive elimination, and finally, reoxidation of Pd(0) to an active Pd(II) catalyst with sodium persulfate (Scheme 2.24). They also suggested that TFA was directly involved into the electrophilic metalation step by enhancing the electrophilicity of the Pd center.



Scheme 2.24. Proposed mechanism for oxidative coupling of *O*-phenylcarbamate.

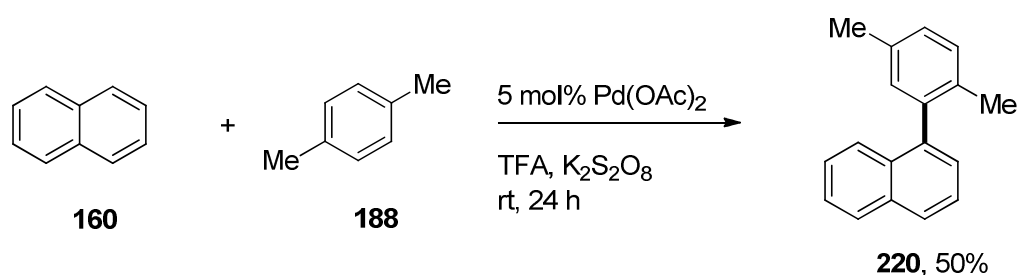
The same year, similarly to Shi and Buchwald's work,^{41,42} Dong and co-workers also described a new palladium catalysed methodology for *ortho*-arylation of phenylacetamides, benzamides, and anilides.⁴⁵ This methodology could be considered as an expansion of the methodology described just above. The authors also managed to crystallise the palladium complexes involved in the reaction and some intramolecular examples were also described (Scheme 2.25).



Scheme 2.25. Palladium catalysed oxidative coupling of anilides, benzamides and phenylacetamides with arenes.

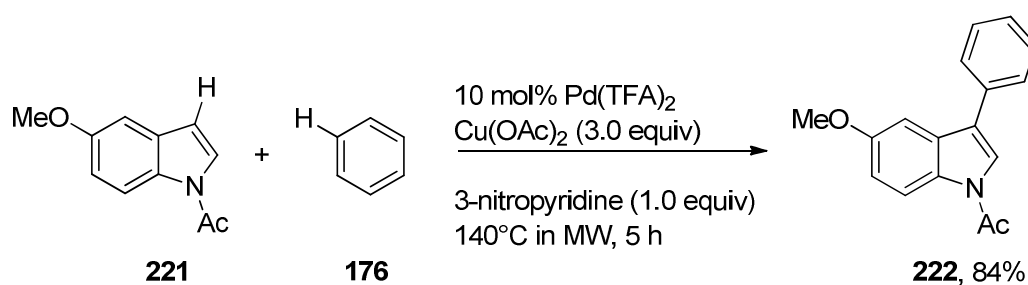
The oxidative arylation of unactivated directing group-free arenes is considered to be more challenging and attractive, as the substrate scope could be enlarged to many more substrates.

Similarly to his work regarding the oxidative dimerization of *p*-xylene,³⁵ Lu and co-workers published a communication on intermolecular dehydrogenative coupling of naphthalene with *p*-xylene. Reaction conditions were identical as the one used in their previous paper and yields of cross-coupled products were moderate (~50%). Still, by tuning the concentration of TFA used in the reaction, the authors were able to gain a selectivity control of the reaction. This was a highly promising result for the catalytic Ar¹-H/Ar²-H cross-coupling reactions (Scheme 2.26).



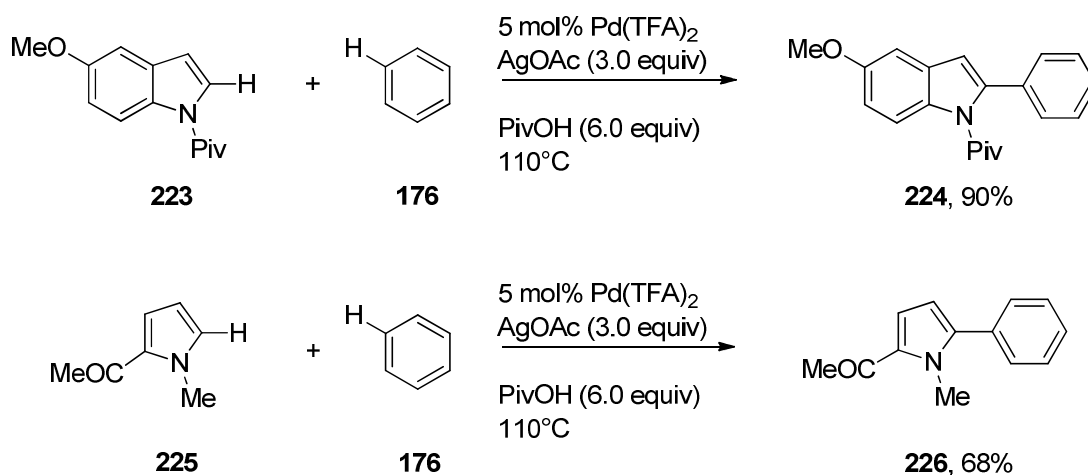
Scheme 2.26. Palladium catalysed intermolecular oxidative coupling of arenes.

In 2007, Fagnou and co-workers reported breakthrough results regarding the intermolecular oxidative arylation of indoles with benzene.⁴⁶ This novel transformation occurred with perfect selectivity control. Indeed, by using a combination of copper acetate as oxidant, catalytic amount of 3-nitropyridine as additive, in the presence of Pd(TFA)₂, the authors could easily discriminate between the arylation at the C(2) or C(3) position of the indole. This specific mixture of reagents allowed the clean arylation of *N*-acetylindoles at the C(3) position (Scheme 2.27). The addition of the palladium at the most nucleophilic position suggested an electrophilic substitution (S_EAr) pathway in first step, then, a concerted metalation-deprotonation (CMD) pathway was proposed to give an Ar¹-Pd^{II}-Ar² species which could easily reductively eliminate to give the final product.



Scheme 2.27. Palladium catalysed intermolecular and selective oxidative coupling of benzene with indoles at the C(3) position.

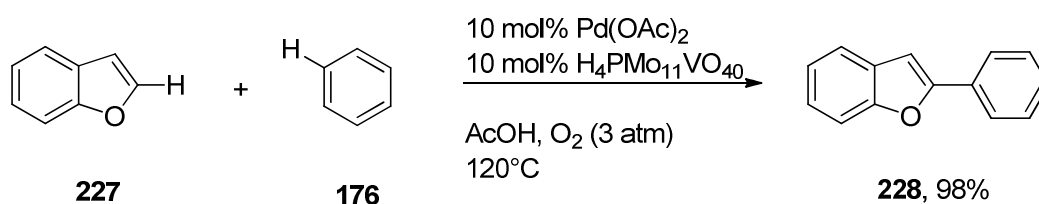
By employing silver(I) acetate as the terminal oxidant in place of copper (II) acetate, the same group reported excellent selectivity for arylation at C(2) position of indoles and pyrroles (Scheme 2.28).⁴⁷ Similar observations were also made by Deboef *et al.*⁴⁸ Fagnou's group suggested that the switch in selectivity was linked to the acetate base. Indeed, when added as silver (I) or caesium (I) salts, the increased selectivity to the Pd-catalyst, was perhaps due to the cleavage of higher order palladium clusters and formation of monomeric palladium species.



Scheme 2.28. Palladium catalysed intermolecular and selective oxidative coupling of benzene with indoles and pyrroles at the C(2) position.

In 2007, Deboef *et al.*, key players in the field of intermolecular oxidative arylation, reported the palladium catalysed oxidative arylation of benzene with benzofuran **227** (Scheme 2.29).⁴⁹ 10 mol% of a co-catalyst named heteropolymolybdovanadic acid H₄PMo₁₁VO₄₀ (HPMV) and molecular oxygen allowed the formation of 2-

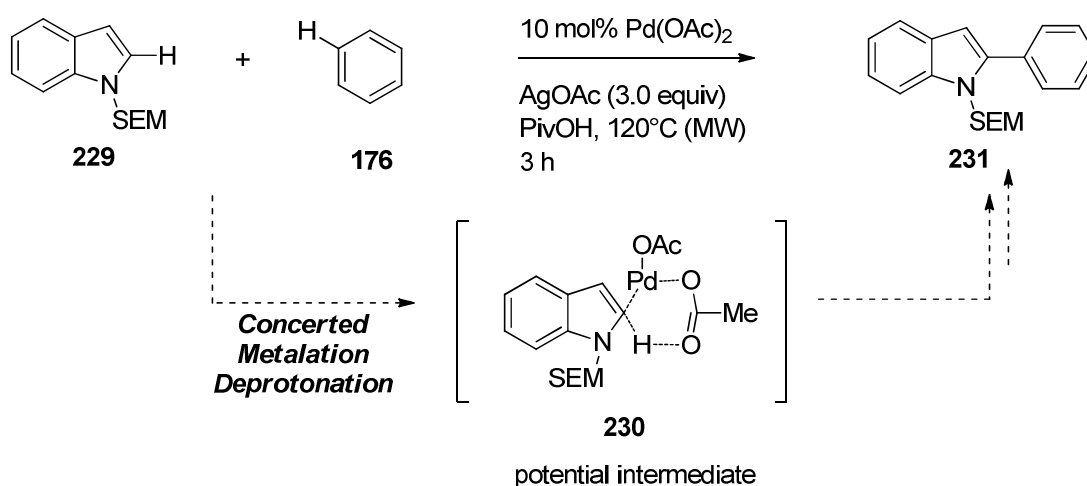
phenylbenzofuran in excellent yield (98%). However, extended reaction times caused the formation of the 2, 3-diarylated product, albeit in low yields.



Scheme 2.29. Palladium catalysed oxidative coupling of benzofuran with benzene.

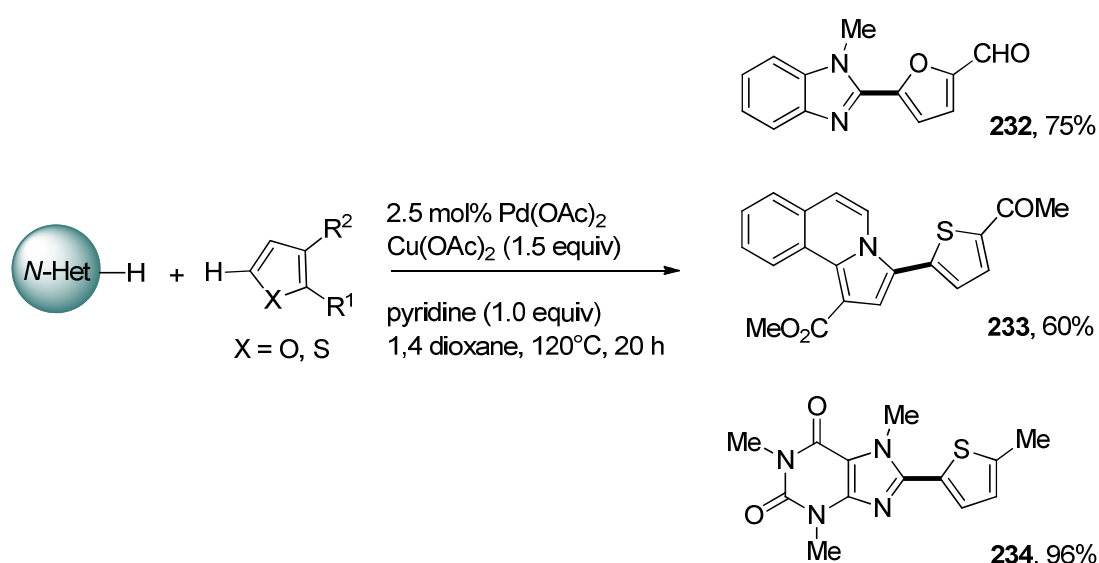
In 2010, Deboef and co-workers contributed to the mechanistic understanding involved in the direct oxidative arylation of *N*-alkylindoles with benzenes (Scheme 2.30).⁵⁰

As it was suggested before by Fagnou and co-workers, experimental and computational data indicated that the mechanism for C-H palladation of both the indoles and arenes could be best described as concerted metalation-deprotonation (CMD). Moreover, the authors hypothesised that the reactivity of the oxidative cross-coupling could be modulated as a function of the medium's acidity. Indeed, they have shown that the regioselectivity of the palladation of indole in oxidative coupling reactions was slightly affected by the acid concentration. However, the acidity of the medium did not significantly affect the CMD process for the palladation of benzenes.



Scheme 2.30. Palladium catalysed oxidative arylation of indole *via* concerted metalation-deprotonation mechanism.

Unusual heterocycles such as xanthines, indolizines, azoles and pyridine *N*-oxides also attracted the attention of the synthetic organic chemists. You *et al.* developed an elegant and powerful way to couple such heteroaromatics with thiophenes and furans (Scheme 2.31).⁵¹ This methodology represents the first example of oxidative coupling reaction involving low catalyst loading (2.5 mol%). This palladium (II) catalysed system has also proven to be perfectly regioselective (Scheme 2.31). Moreover, it is notable that only 3 equivalents of thiophenes or furans compared to the other heterocycle were used in the transformation. This work represents a real step forward in oxidative cross-coupling reactions since previous works required 30 to 40 equivalents of arenes compared to the other substrate. This is even more surprising because as we mentioned previously, such electron-rich five-membered heteroarenes are susceptible to oxidative homocoupling in the presence of palladium (II). But, in this case heterocoupled products were formed more rapidly than homocoupled.

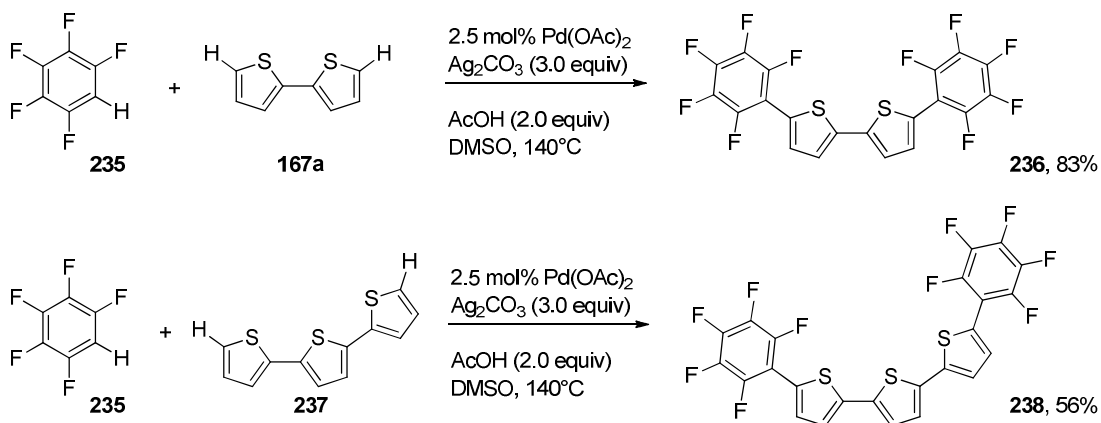


Scheme 2.31. Palladium catalysed oxidative coupling of xanthines, indolizines and azoles with thiophenes and furans.

A last example of catalytic double C-H bonds activation and oxidative coupling of heterocycles with arenes has been reported by Zhang and co-workers. The authors described the straightforward and practical method for palladium acetate catalysed cross-coupling of electron-deficient perfluoroarenes with furans, thiophenes and

indoles.⁵² The reaction which only required 2.5 mol % of catalyst proved to be very efficient, chemo- and regioselective. Furthermore, as the C-H bond of perfluoroarenes was activated, the palladation of the perfluoro-species could occur easily and the system only required a small excess of perfluoroarenes (3 equiv.).

To demonstrate the synthetic application of this methodology, the authors successfully prepared in higher yield than the traditional techniques,⁵³ n-type organic semiconductors **236** and **238** in only one step (Scheme 2.32).



Scheme 2.32. Palladium catalysed oxidative coupling of perfluoroarenes with thiophenes.

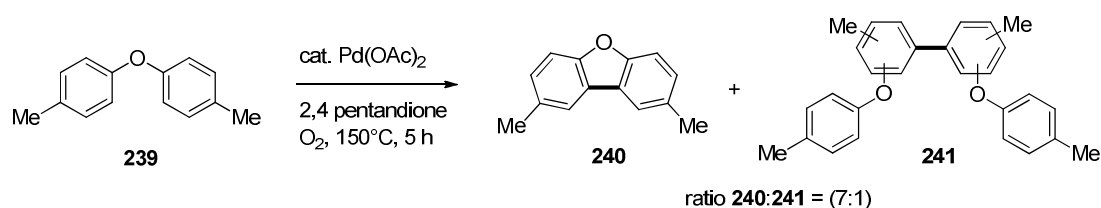
2.2.3.2 Intramolecular oxidative coupling

Intramolecular oxidative coupling have been reported since the early ages of oxidative arylations as a route to simple polycyclic ring systems. Indeed, oxidative cyclisation represents a method of choice for a rapid entry to biologically active scaffolds such as carbazoles, dibenzofurans and cyclic amides. However, in most of the cases, intramolecular dehydrogenative coupling systems were not directly studied on their own, but most of the time, briefly mentioned in systems focused on intermolecular reactions.

The section below will be focused on the report of intramolecular oxidative transformations for the synthesis of 5- and 6-membered polycyclic ring systems. Additionally, the synthetic transformations will be organised depending on the nature of the ring systems formed.

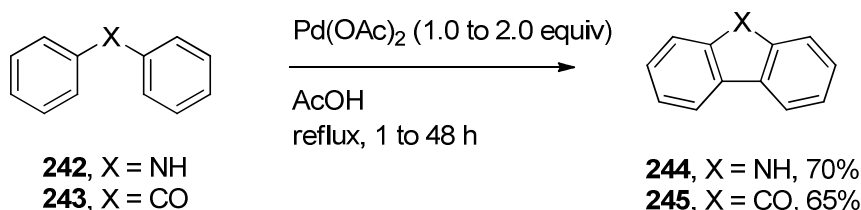
2.2.3.2.1 Dibenzofurans and carbazoles

One of the earliest examples of palladium catalysed intramolecular oxidative cyclisation was reported by Hitatani in 1974.⁵⁴ In this seminal study, 2,8-dimethyldibenzofuran **240** was prepared by treating the corresponding di-*p*-tolyl ether **239** in the presence of catalytic amounts of palladium acetate at 150 °C (Scheme 2.33). The authors also noticed that the substitution pattern on the benzene rings and the solvent used drastically affected the formation and the ratio of dibenzofurans / homocoupling products.



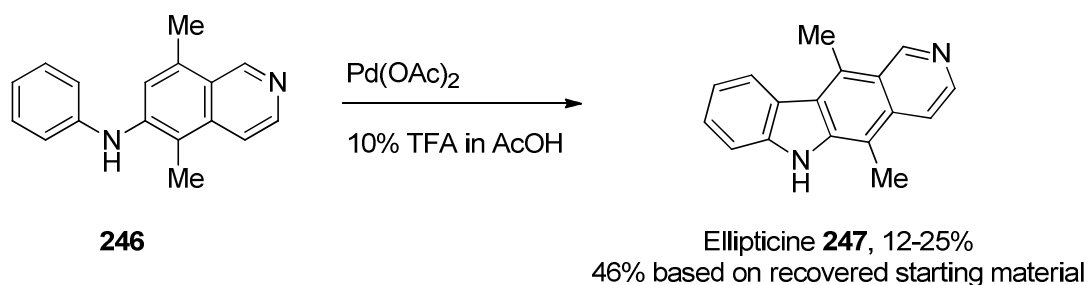
Scheme 2.33. Palladium catalysed intramolecular oxidative coupling of diphenyl ethers.

The carbazole scaffold was one of the most targeted structure by synthetic chemists due to its biological interest.^{55,56} Indeed, chemists such as Akermarck and co-workers have worked on the oxidative cyclisation of diphenylamine **242** to carbazole **244** since the 1970s.⁵⁷ However, stoichiometric or excess amount of palladium acetate had to be used to obtain good yields (Scheme 2.34). The methodology was also extended to the oxidative cyclisation of diphenyl ethers, benzophenone and benzanilide.



Scheme 2.34. Stoichiometric oxidative cyclisation of diphenylamine and benzophenone.

Another early report of carbazoles synthesis was made by Miller *et al.* in 1980. Oxidative cyclisation of anilinoisoquinoline **246** was used in the last step of the synthesis of the anticancer drug, ellipticine **247** (Scheme 2.35).⁵⁸ The approach proved to be successful although the yields were not outstanding. Moreover, the cyclisation of anilinoisoquinoline **246** required one or two equivalents of palladium acetate in TFA / AcOH solvent mixture. Although the yield of this final step was moderate, the overall yield of the ellipticine synthesis was at that time competitive with other synthetic approaches which did not involved intramolecular oxidative coupling reactions.

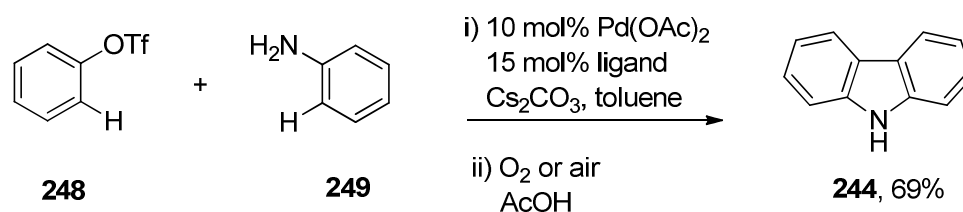


Scheme 2.35. Synthesis of ellipticine *via* oxidative cyclisation.

More recently, a one-pot synthesis of simple carbazoles *via* palladium catalysed *N*-arylation and oxidative coupling have been reported by Fujii and Ohno in Japan.⁵⁹

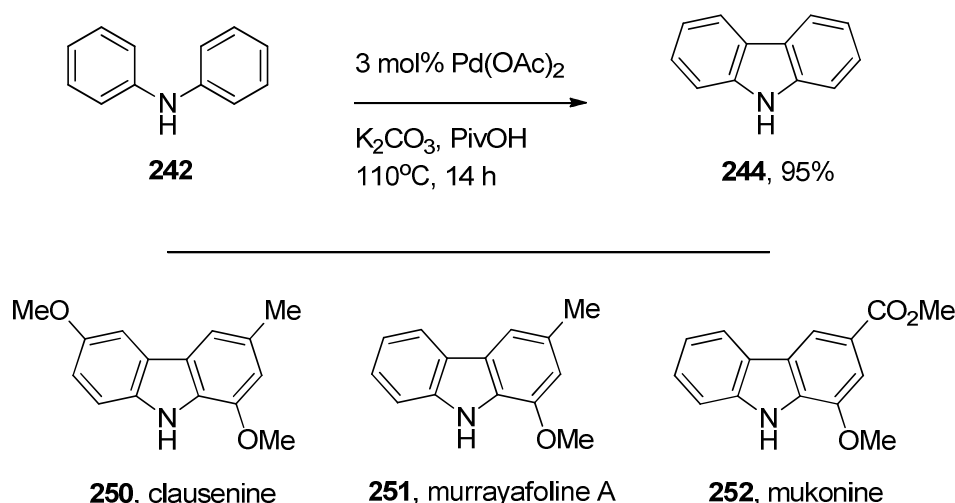
The authors developed an elegant methodology for the direct construction of carbazoles by coupling aryl triflates **248** and anilines **249**, through one-pot palladium catalysed Buchwald–Hartwig *N*-arylation and oxidative coupling in the presence of molecular oxygen or air (Scheme 2.36).

The first step, Pd(0) catalysed, was carried out in toluene in the absence of oxidant, then acetic acid and oxygen were introduced into the crude mixture to oxidize Pd(0) to Pd(II) and permitted the oxidative cyclisation step to occur. Yield recorded for that transformation were generally good and this work could be considered as one of the first palladium catalysed intramolecular oxidative coupling methodology which was truly efficient.



Scheme 2.36. One-pot synthesis of carbazoles by palladium catalysed *N*-arylation and oxidative coupling.

Almost at the same time, in 2008, Fagnou and co-workers reported the development and the scope of palladium (II) catalysed oxidative biaryl synthesis under air.⁶⁰ Fagnou compared the solvent effect on the oxidative cyclisation of diarylamines and noticed that the use of pivalic acid instead of acetic acid as the reaction solvent resulted in broader substrate scope, higher yields and greater reproducibility. By isolating undesired by-products from reactions carried out in acetic acid, the authors could identify the competing reaction pathways when the reaction was performed in acetic acid. Fagnou *et al.* illustrated the power of their optimised reaction conditions to the synthesis of three naturally occurring electron-rich carbazoles: Clausenine **251**, Murrayafoline A **250** and Mukonine **252** (Scheme 2.37).



Scheme 2.37. Palladium catalysed intramolecular oxidative coupling of diarylamines in pivalic acid.

2.2.3.2.2 Pyrroles and indoles

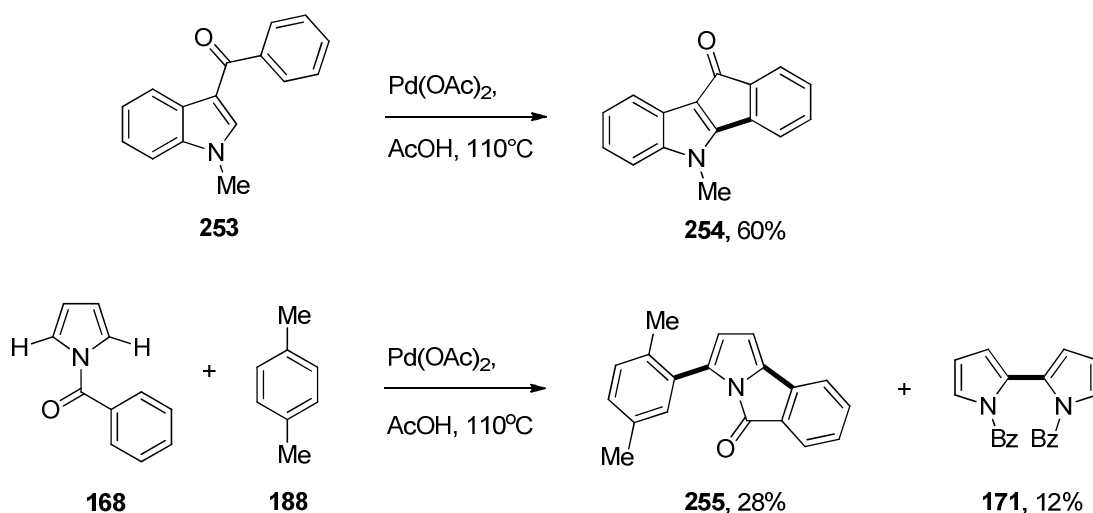
Pyrroles and indoles are considered as privileged structures in numerous research areas such as: pharmaceuticals, fragrances, agrochemicals, pigments, and material sciences.⁶¹

Indole chemistry received particular interest since the mid-1950s when the alkaloid reserpine⁶² was introduced as one of the first drugs for the treatment of diseases of the central nervous system (CNS). Enormous efforts have been devoted to the development of efficient synthetic routes for the preparation and direct functionalisation of these heteroaromatic compounds.⁶³

Biological potentials of benzannulated nitrogen containing heterocycles attracted organic chemists to develop new approaches for the synthesis of annulated heteroarenes.⁶⁴⁻⁶⁷ However, the formation of benzannulated indoles and pyrroles by double C-H bonds activation and oxidative cyclisation has not been extensively reported.

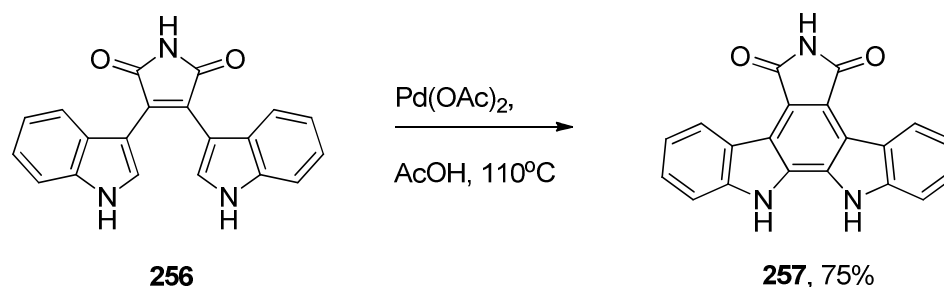
Once again, Itahara and co-workers were one of the pioneers to use dehydrogenative cyclisation reactions for the synthesis of benzofused *N*-heterocycles. In 1978, his group reported the first intramolecular ring closure reaction by synthesising in 60% yield the tetracyclic compound **254** from 3-benzoyl-1-methylindole **253** using palladium acetate.⁶⁸ Indoles substituted at the C(3) selectively cyclised at the C(2)

position creating a new C_{Ar}-C_{Ar} bond (Scheme 2.38). Subsequently, in 1985, while investigating the intermolecular oxidative coupling of *N*-benzoyl-pyrroles with arenes, Itahara and co-workers isolated in some cases the products of intramolecular C-H / C-H coupling along with homocoupling products (Scheme 2.38).³³



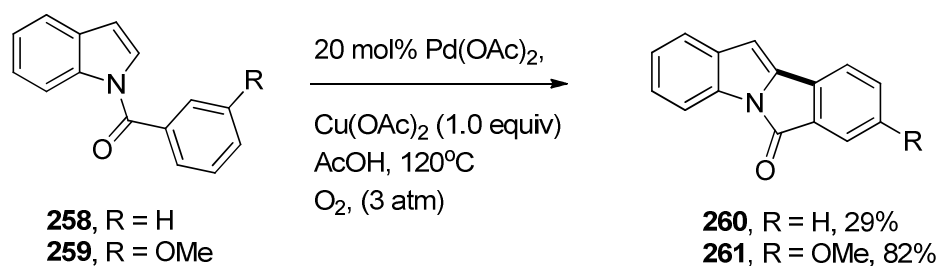
Scheme 2.38. Itahara's contributions to intramolecular oxidative couplings of indoles and pyrroles.

During the 1990s, Hills *et al.* used a similar palladium mediated cyclisation process to achieve the short synthesis of the core of the protein kinase inhibitor natural product Staurosporine.⁶⁹ Treatment of arcyriarubin A **256** with stoichiometric amount of palladium acetate in acetic acid reflux for 18 hours gave the expected product **257** in 75% yield (Scheme 2.39). However, despite the fact that the cyclisation represented one of the earliest example of construction of central six-membered ring of indolo[2,3-a]carbazole system by oxidative coupling, the reaction was not catalytic.



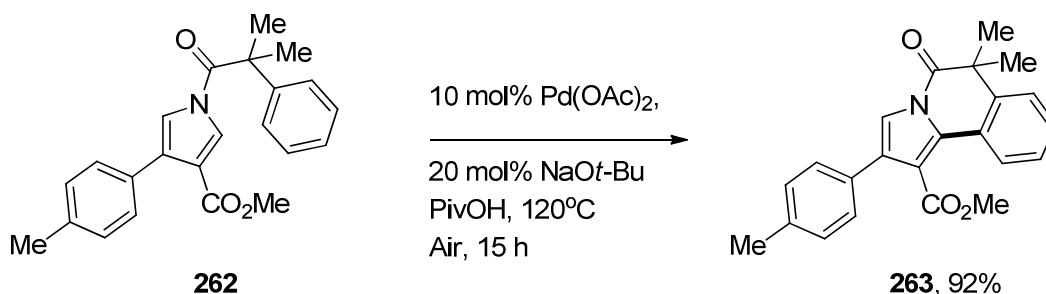
Scheme 2.39. Synthesis of the staurosporine core *via* oxidative cyclisation.

DeBoef *et al.* reported very briefly in 2007, the aerobic catalytic oxidative cyclisation of *N*-benzoylindole derivatives.⁴⁹ Two interesting observations could be made. The first one was that the cyclisation did not seem favourable as the transformation required a high catalyst loading (20%) and the product **260** was obtained in low yield. The second observation was that the electronics on the molecule seemed to play a critical role. Indeed, when an electron-donating group was added to the tethered arene, the yield nearly tripled **261**. This encouraged the authors to postulate that the palladation of arene could proceed *via* an electrophilic pathway (Scheme 2.40).



Scheme 2.40. Palladium catalysed intramolecular dehydrogenative coupling of *N*-benzoylindoles.

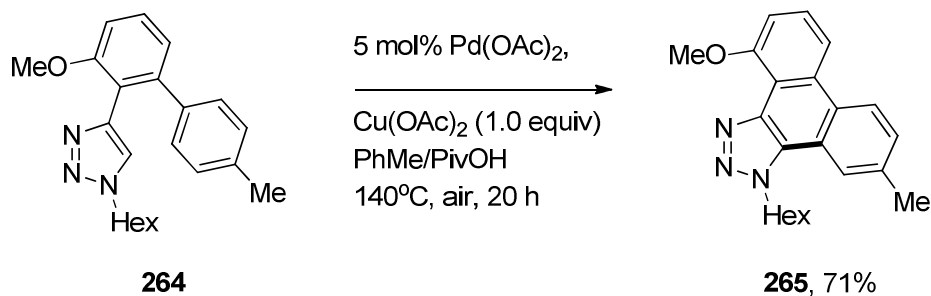
One year later, Fagnou's group described the palladium catalysed intramolecular coupling of activated pyrroles with unactivated alkanes in air.⁷⁰ Although this paper was mainly focused on the challenging oxidative coupling of $\text{C}_{\text{sp}^3}\text{-H}$ with $\text{C}_{\text{sp}^2}\text{-H}$, the authors reported one example of intramolecular $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^2}$ bond formation. In this competitive experiment, the reactivity of terminal $\text{C}_{\text{Alkane-H}}$ and $\text{C}_{\text{Aromatic-H}}$ bonds was directly compared towards C-H activation (Scheme 2.41). As expected, $\text{C}_{\text{sp}^2}\text{-H}$ bond was more reactive than the $\text{C}_{\text{sp}^3}\text{-H}$ bond and only one product was isolated in excellent yield.



Scheme 2.41. Six membered ring oxidative cyclisation reaction.

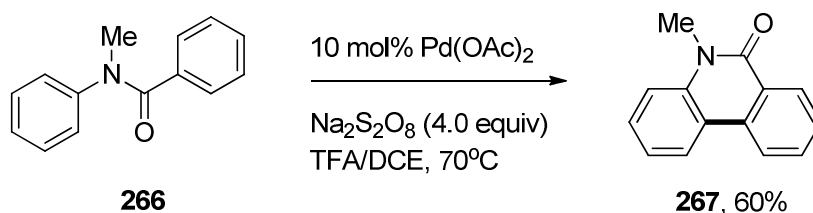
2.2.3.2.3 Six-membered ring oxidative ring closure reactions

Although most of the literature on oxidative cyclisations reports the formation of a new five-membered ring, two groups developed two different palladium catalysed cyclisation systems to construct six-membered rings. Intramolecular oxidative direct arylation on 1,2,3-triazoles was investigated by Ackermann and co-workers in 2010.⁷¹ The system used allowed to prepare benzofused-triazole derivatives containing a central 6-membered ring and the methodology was extended to the rapid preparation of π -conjugated heteroannulated phenanthrenes (Scheme 2.42).



Scheme 2.42. Palladium catalysed intramolecular oxidative coupling of 1,2,3-triazole with arenes.

The most recent example of 6-membered ring formation by oxidative ring closure was reported by Dong and co-workers in 2010. They worked on the catalytic intramolecular oxidative *ortho*-arylation of benzanilides **266** (Scheme 2.43).⁴⁵ It is worth mentioning that this type of transformation had also been realised in 1975 by Akermark *et al.* using stoichiometric amount of palladium instead.⁵⁷ Although the fact that both transformations were identical, reaction conditions were not. Dong's group used a combination of dichloroethane and TFA as solvents instead of acetic acid, and used sodium persulfate as the oxidant instead of oxidant-free conditions for Akermark.



Scheme 2.43. Palladium catalysed intramolecular oxidative *ortho*-arylation of benzanilides.

2.2.4 Literature summary and emerging idea

Palladium mediated oxidative coupling of arenes represents in theory the ultimate way to couple aromatic identities together as no pre-functionalisation of both partners are required. Unactivated C-H bonds can react to form a new C-C bond and simple hydrogen is released out of the reaction system as waste. This method of cross-coupling attracted from the late 1960s to 1980s, a first set of chemists, who developed and optimised the first stoichiometric and later catalytic, palladium mediated cross-coupling reaction of arenes and heteroarenes. The transformations studied were generally not high yielding and were essentially focused on simple substrates as chemists faced the challenging problem of the selectivity of the reaction. More recently, from 2001 until now, chemists have managed to get better regio- and selective control of the reaction.^{8,46} Indeed, reaction conditions improved and specific C-H bond could be accurately targeted allowing better efficiency. These reaction optimisations permitted to increase the scope of the reaction to intermolecular and intramolecular oxidative arylations. As mentioned before, intermolecular dehydrogenative coupling reactions have captivated more attention than intramolecular oxidative cyclisations. Indeed, arylation between arenes / arenes, heterocycles / arenes and heterocycles / heterocycles have been well investigated, only a few simple and redundant intramolecular systems have been studied so far. These systems based of 5- or 6-membered oxidative ring closure permitted the synthesis of biologically and electronically valuable scaffolds such as carbazoles, dibenzofurans and highly conjugated benzofused heterocycles.

Considering the fact that benzofused aromatics are valuable molecules⁷² and that the literature on dehydrogenative cyclisations only reports the formation of new five or six membered rings, we were sufficiently encouraged to develop a new methodology for the synthesis of medium-sized benzannulated aromatics by oxidative C-H / C-H coupling.

2.2.5 Benzannulated medium ring heterocycles

Medium-sized benzofused heterocycles such as biologically active benzazepine or benzodiazepine class of molecules have received considerable attention by chemists and the pharmaceutical industry. For example, the medium-sized Amaryllidaceae alkaloid, (-)-pancracine **268**, has weak hypotensive and anti-convulsive activities,⁷³ and, diazepam **67**, well known as Valium, possesses biological activities on the central nervous system such as decreased anxiety, hypnosis and sedation (Figure 2.2).⁷⁴

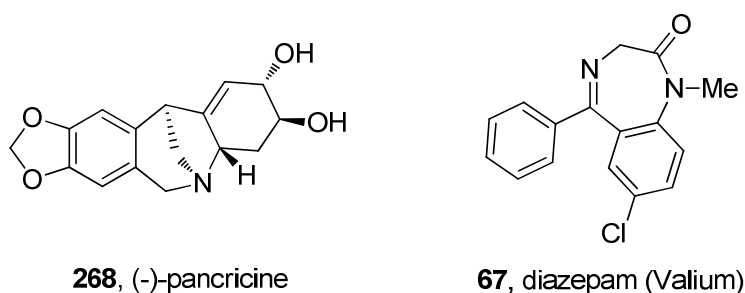


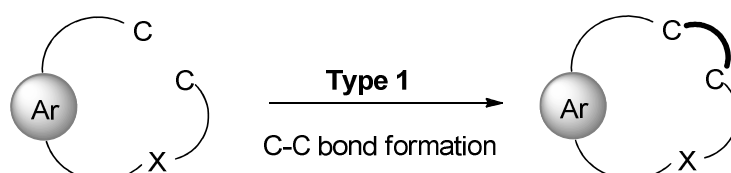
Figure 2.2. Example of biologically active medium ring benzazepine and benzodiazepine.

The term “medium ring” first introduced by Prelog and Brown⁷⁵ usually referred to cyclic molecules having a ring size in the range 8 to 11. Moreover, when analysing the conformational effect within these ring systems, 7- and 12-membered rings are also considered as medium rings.

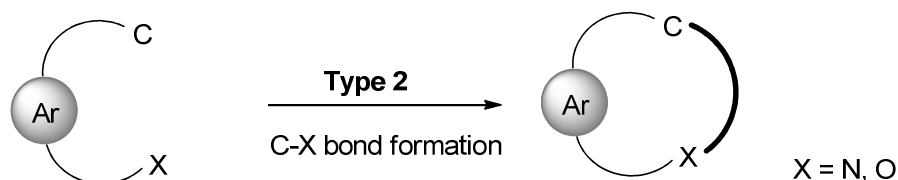
In such ring systems, it is also important to notice that, large transannular strains due to repulsive interactions between the methylene groups across the ring exist. These repulsive effects combined with the important entropic / enthalpic factors related to the formation of these ring make the synthesis of medium rings difficult. Such thermodynamic factors become even more marked when dealing with eight- and nine-membered rings, making these rings the most difficult to prepare by conventional cyclisation methods.⁷⁶

Currently, the methodologies available for the preparation of such ring systems still remain very specific. Although, cycloaddition, ring expansion and annulation strategies proved to be successful methods for the synthesis of these structures, the cyclisation approach still remains an important challenge for synthetic chemists.^{77,78}

Cyclisation processes could be classified in two major categories whether the cyclisation occurs either through C-C bond formation (Type 1) or C-X (X = N, O) bond formation (Type 2 in Scheme 2.44). The first category refers to radical reaction, olefin metathesis or palladium mediated intramolecular C-C bond formation. The second (type 2) involves palladium (0) catalysed aryl amination and intramolecular etherification of aryl (pseudo)halides.⁷⁹



i.e. radical reaction, olefin metathesis or palladium catalysed C-C bond formation



i.e. palladium catalysed aryl amination and intramolecular etherification

Scheme 2.44. Two possible pathways for the synthesis of benzofused medium ring heterocycles.

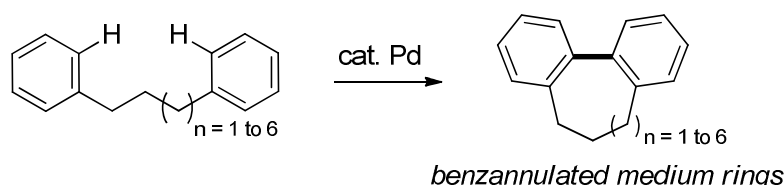
As a precise description of synthetic methods of preparation of benzannulated medium rings would be too long beyond the topic of my thesis, I will not review this particular field. However, if the reader desires to get more details on this topic, Chattopadhyay and co-workers have written an excellent review, which covers works published between 1996 and 2007.⁸⁰

2.2.6 Project idea

In dealing with medium-sized ring formation through oxidative coupling, two main challenges have to be pointed out. The first challenge would be that medium rings are difficult to synthesise due to their large activation energy barrier.^{76,81} The second challenge refers to the oxidative coupling itself and more precisely to the palladation of the substrate which could be in some cases very difficult to do and/or to control depending on the substrate reactivity.

Therefore, combining these two aspects (medium ring formation and substrate palladation) could result in a very difficult way to prepare medium ring systems.

For example, the cyclisation of two simple unactivated aromatics linked by a long aliphatic chain could be very difficult to do as the activation energy needed to achieve the ring closure would be large (Scheme 2.45).



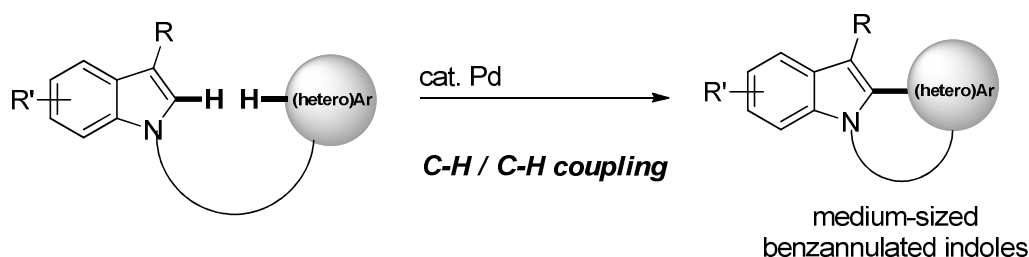
Scheme 2.45. Benzannulated medium rings formed by palladium catalysed oxidative cyclisation.

To achieve our goal, we decided to simplify the system by designing a substrate which would be easily palladated. Indeed, if the palladation of the substrate becomes an easy task, the cyclisation would only then depend on the thermodynamic aspect of the medium ring formation.

2.2.6.1 Substrate choice

Reactivity and selectivity of indoles in cross-coupling reactions have been extensively studied and are well understood.^{11,63,82} In the past, indoles proved to be very good partners for oxidative coupling reactions.^{33,46,49,69} Moreover, the selectivity of the arylations at the C(2) or C(3) positions can easily be controlled and triggered by simple switches of *N*-protecting group⁸³ or oxidants.^{38,39,47,48,50} Additionally, indoles are fairly stable scaffolds under oxidative reaction conditions and are easily functionalisable which represents a plus for starting material preparations.

Considering all that, we decided to use the indole scaffolds as versatile building blocks to develop a new methodology for medium-sized rings synthesis by palladium catalysed oxidation cyclisation of heteroarenes – arenes. The following scheme (Scheme 2.46) highlights the general idea of making medium-sized benzannulated indoles by double C-H bonds activation.



Scheme 2.46. General idea of the project.

2.2.6.2 Potential synthetic targets

We were pleased to notice that the same kind of medium-sized polycyclic indole cores that we aimed to prepare have already been reported and studied for their biological activities. For instance, the molecule **269a** showed selective binding affinities to the mitochondrial diazepam-binding inhibitor receptor complex (mDRC) and facilitated the transport of cholesterol from the outer to the inner mitochondrial membrane, where a specific type of cytochrome catalysed the side chain cleavage of cholesterol to form pregnenolone.⁸⁴ Another example, compound **269b** (figure 2.3) was shown to act as a specific melatonin receptor (MT2) antagonist.⁸⁵

Series of pentacyclic and tetracyclic inhibitors of hepatitis C virus have also been reported by Koch and Narjes.^{86,87} Out of the biological studies performed, two compounds, **269c** and **269d**, presented high activities in the enzyme as well as cell-based assays and compound **269d** has shown sufficient biological properties to progress as a pre-clinical candidate for treatment of hepatitis C (Figure 2.3).

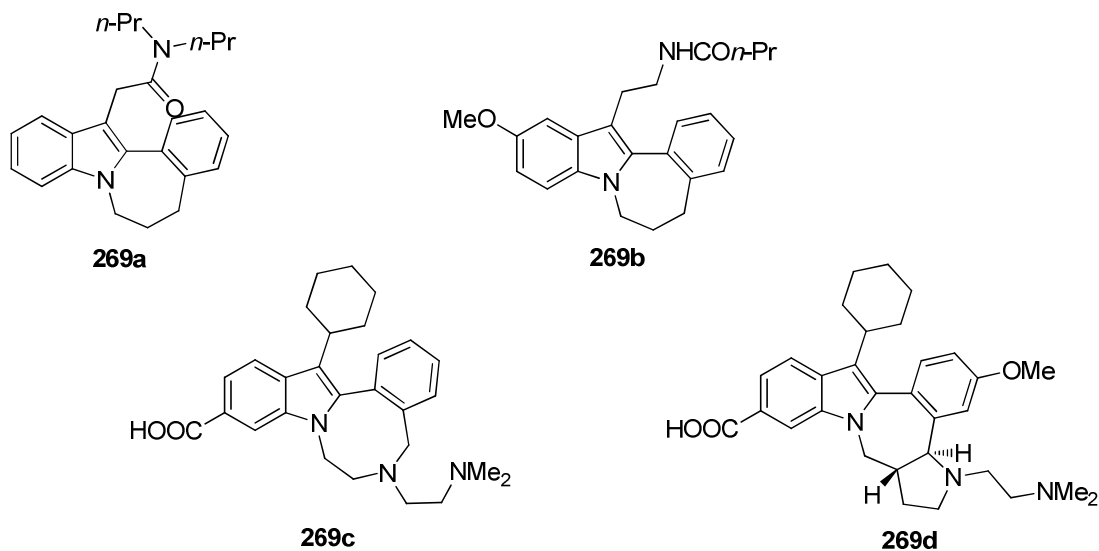


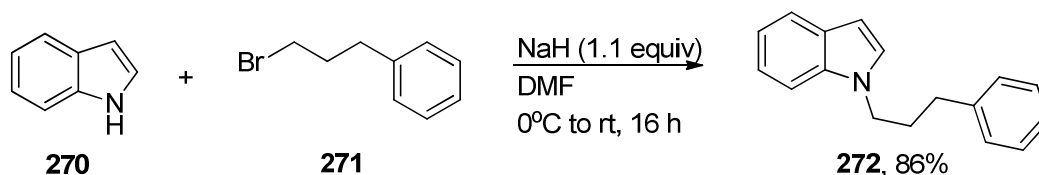
Figure 2.3. Example of biologically active benzannulated polycyclic indoles.

2.3 Results and discussion

2.3.1 Initial screening and optimisation

The exciting structures shown in the previous section encouraged us to prepare indole substrates having a tethering chain connected to the nitrogen atom, and to carry out cyclisation at the C(2) position of the indole. Furthermore, 7-membered ring closure systems were studied in the first place.

Starting material **272** was readily prepared in multi-gram scale in 86% yield from simple starting materials and stoichiometric amount of sodium hydride in DMF using a known procedure (Scheme 2.47).⁸⁸

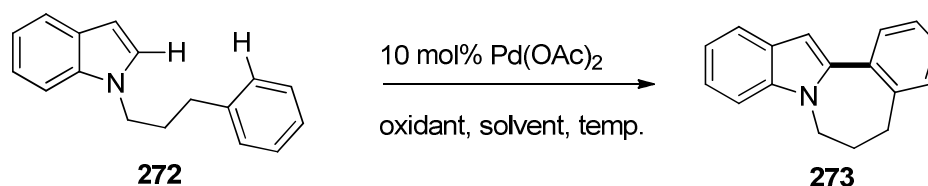


Scheme 2.47. Starting material synthesis *via* indole alkylation reaction.

Having the starting material **272** in hand, we set out to test the possibility of oxidative cyclisation under palladium catalysis. Initial attempts were commenced and results are presented in table 2.1.

As in any methodology project, a screening of several organic solvents, temperatures, oxidants as well as base was initiated and all reactions were monitored by LCMS and TLC.

Table 2.1. First oxidative cyclisation screening of organic solvents and other variables.



| Entry | Oxidant (equiv.) | Solvent [ratio] | Temp. (°C) | Product 273 (%) | Observation |
|-------|---|------------------------|---------------|--------------------|-------------------------|
| 1 | Ag ₂ CO ₃ (2.0) + air | PivOH | 100 | n.d. | Isatin 274 , 49% |
| 2 | Ag ₂ CO ₃ (2.0) | Toluene | 100 | n.d. | S.M. + 275 , 9% |
| 3 | Ag ₂ CO ₃ (2.0) | Mesitylene | 140 | n.d. | S.M. + 275 < 10% |
| 4 | Ag ₂ CO ₃ (2.0) | Chlorobenzene | 100 | n.d. | S.M. + 275 < 10% |
| 5 | Ag ₂ CO ₃ (2.0) | 1,4-dioxane | 100 | n.d. | S.M. left |
| 6 | AgOAc (2.0) | 1,4-dioxane | 100 | n.d. | S.M. left |
| 7 | Ag ₂ CO ₃ (2.0) | CH ₃ CN | 80 | n.d. | S.M. only |
| 8 | Ag ₂ CO ₃ (2.0) | THF | 80 | n.d. | S.M. only |
| 9 | Ag ₂ CO ₃ (2.0) | DMF | 100 | n.d. | Decomp. |
| 10 | Ag ₂ CO ₃ (2.0) | DMSO | 100 | n.d. | Decomp. |
| 11 | AgOAc (2.0) | 1,4-dioxane/TFA [3:1] | 100 | n.d. | S.M. + 275 < 10% |
| 12 | AgOAc (2.0) | 1,4-dioxane/AcOH [3:1] | 100 | n.d. | S.M. + 275 < 10% |
| 13 | Cu(OAc) ₂ (2.0) | 1,4-dioxane/AcOH [3:1] | 80 | n.d. | S.M. + 275 < 20% |
| 14 | Cu(OAc) ₂ (2.0) | DMF/DMSO [9:1] | 80 | n.d. | 275 , 86% |

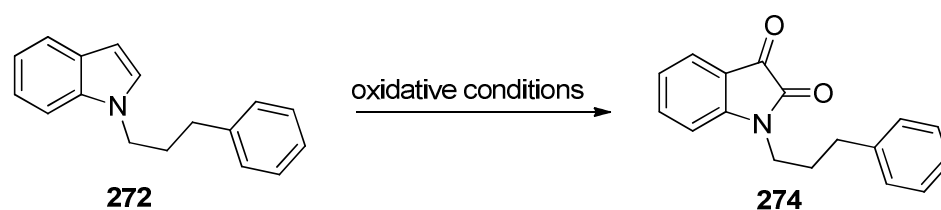
Preliminary screening showed that no reaction happened in the reaction conditions tested. Additional reaction time up to 48 hours did not provide any desired product and none of the product could be detected by LCMS analysis.

However, with the exception of THF and acetonitrile (entry 7 and 8), where the starting material was fully recovered, the substrate was generally reactive enough to be decomposed and/or consumed.

Interestingly, in the presence of pivalic acid, air and excess silver carbonate as oxidant, the indole starting material has been oxidised to an isatin derivative **274**.

This reaction has been previously reported when indoles were treated under strong oxidative conditions such as oxidation with chromium oxide⁸⁹, IBX and indium(III) chloride as lewis acid,⁹⁰ but also when treated with catalytic ruthenium (II) porphyrin complexes.

In our case, it is not defined yet, which active species promoted the oxidation of **272** to **274** (Scheme 2.48).



Scheme 2.48. Oxidation of indoles to isatins.

Additionally, two notable features appeared while treating starting material with substituted benzene solvents.

Firstly, no products from the intermolecular reaction between the aromatic solvents and the indole were isolated. A similar observation was made before by Fagnou and co-workers and they showed that pivalic acid or other organic acids such as acetic acid or TFA were needed for the reaction to happen in an intermolecular fashion between benzenes and indoles.

The other remarkable point was that small amount of unsymmetrical dimeric indole **275** were isolated. This bisindole product could be isolated to different extents in almost all the conditions screened. Surprisingly, although mixing silver carbonate and polar solvents such as DMF or DMSO resulted in complete decomposition of the starting material, conditions where DMF and DMSO were used along with copper acetate gave the compound **275** in 86% yield.

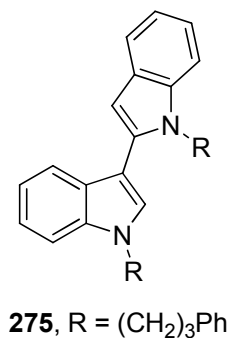


Figure 2.4. Dimeric indole species **275** isolated.

Entries 9, 10 and 14 in table 2.1 shows that copper acetate tend to better promote the formation of 2,3'-linked biindoles than silver acetate and that the formation of 2,2'- or 3,3'-biindoles isomers were not favoured under these reaction conditions.

These early results were perfectly in accordance with what has been very recently explored by Zhang and Shi.^{38,39} In fact, by optimising the reaction conditions, they noticed that silver salts would promote the formation of 2,2'-biindoles whereas copper salt would favour 2,3'-biindoles.

Thus, the initial screening performed indicated that starting material was reactive enough under reaction conditions tried but no desired product could be detected. Moreover, unexpected and unwanted dimerization reaction indicated that the position C(3) of the indole also known as the most nucleophilic position could interfere in our attempt to activate and functionalise the position C(2). Therefore, to avoid any problem of reactivity of the position C(3), indoles having the 3-position blocked were prepared.

It was decided that a slightly electron-donating group (3-methyl), an electron-withdrawing group (3-carboxyaldehyde) and a directing-group (3-CH₂NMe₂) were to be used to test the applicability of this chemistry. 3-Methylindole, indole-3-carboxyaldehyde and gramine were cheap and readily available precursors for the synthesis of these *N*-alkylated products **276**, **277** and **278**.

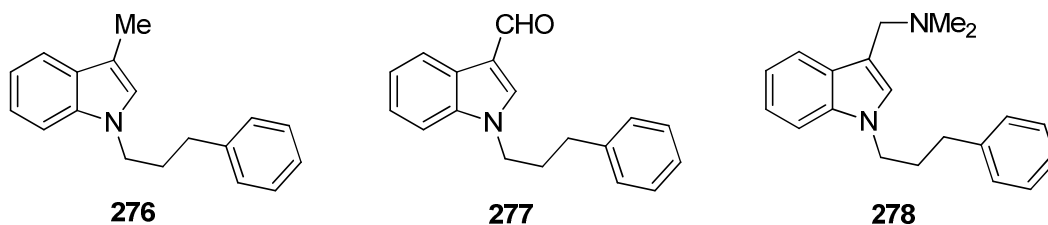
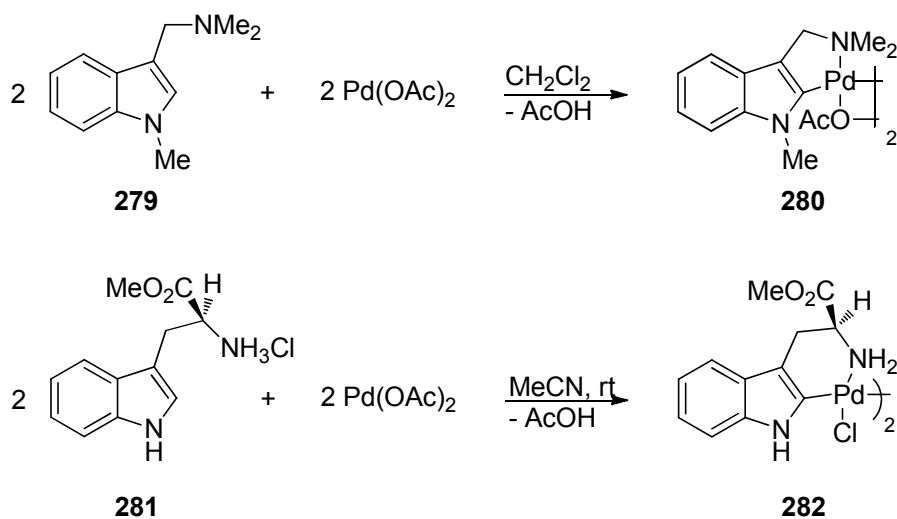


Figure 2.5. Selection of 3-substituted indole starting materials.

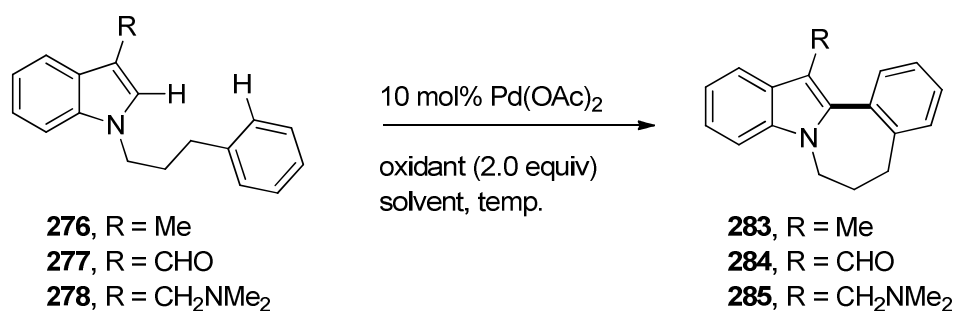
Along with the inexpensive cost of making compound **278**, this starting material was chosen specifically because of its known capability to direct the palladation of indole at the position C(2). Indeed, the presence of the tethered donor group, dimethyl amine (NMe₂), could allow the initial coordination of the ligand (NMe₂) to the metal and could favour the activation of the C-H bond at the C(2) position. Regiospecific cyclometalation of indole alkaloids such as gramines,^{91,92} tryptamines or

tryptophans⁹³ have been successfully achieved under generally mild reaction conditions (Scheme 2.49).



Scheme 2.49. Cyclometalation of *N*-methyl gramine and L-tryptophan methyl ester hydrochloride.

Table 2.2. Screening of organic solvents and other variables for oxidative cyclisation of 3-substituted indoles



| Entry | S.M. | Oxidant | Solvent | °C | Product |
|-------|------------|--|---------|-----|--|
| 1 | 278 | Ag ₂ CO ₃ | MeCN | 80 | 277 : 80% isol. + 284 : 7% isol. |
| 2 | 278 | Cu(OAc) ₂ | MeCN | 80 | 277 ~ 80% + 284 : 5% isol. |
| 3 | 278 | TBHP | MeCN | 80 | Decomp. + 277 obs. |
| 4 | 278 | K ₂ S ₂ O ₈ | MeCN | 80 | Decomp. |
| 5 | 276 | Cu(OAc) ₂ | Toluene | 110 | S.M. |
| 6 | 276 | Cu(OAc) ₂ | MeCN | 80 | S.M. + 277 obs. |
| 7 | 276 | Cu(OAc) ₂ | DMF | 110 | S.M. + 284 : 9% isol. |
| 8 | 277 | Ag ₂ CO ₃ | MeCN | 80 | S.M.: 74% isol. + 284 : 10% isol. |
| 9 | 277 | Cu(OAc) ₂ | DMF | 110 | S.M. + 284 : 18% isol. |

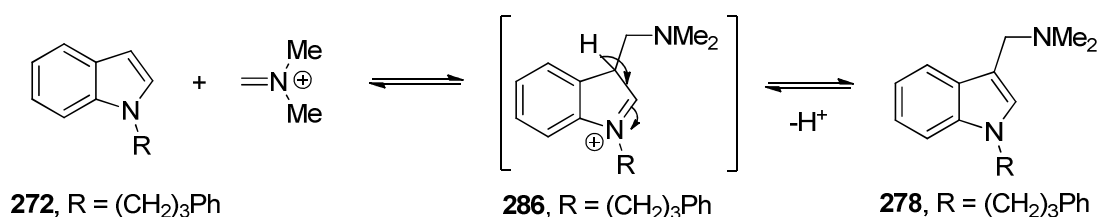
A screening with more than thirty reaction conditions has been carried out. Considering the fact that a lot of reactions turned out to give identical results, table 2.2 only shows a selection of screening conditions relevant for discussion and further reaction optimisations.

It was previously mentioned that cyclopalladated gramines could easily be prepared at room temperature or under mild conditions of temperature. Thus, compound **278** was generally subjected to reaction using low boiling solvents such as acetonitrile, dichloroethane or THF. Entries 1 to 4 show the results obtained when acetonitrile was used and oxidants varied.

By looking at the table 2.2 the reader can observe that starting materials **278** and **276** did not afford any of the expected medium-sized cyclised products **285** and **283**. Indeed, in all the reaction conditions used, these two starting materials were either recovered at the end of the reaction or converted to unexpected products (entries 1 to 7). Spectroscopic data analysis of the major product isolated in entries 1 and 2 indicated that the gramine compound **278** was oxidised to compound **277** and in some cases, isolated yield for **277** increased up to 80%.

These surprising results could be rationalised by the fact that the methylene group at the allylic position of the gramine was very activated and therefore easily oxidised.

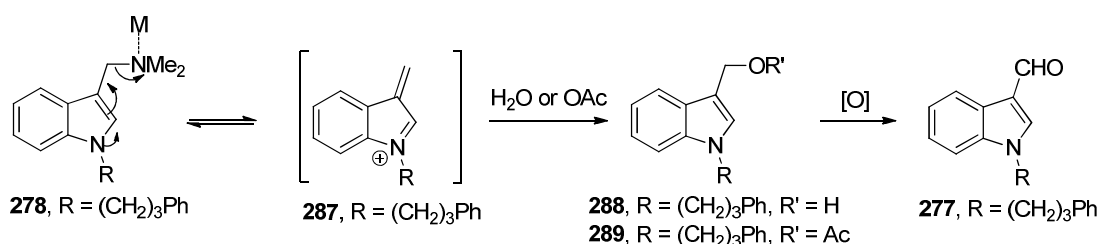
One possible explanation for the starting material decomposition could be that the gramine derivative **278**, Mannich base from the reaction between the corresponding indole, dimethylamine and formaldehyde, underwent a metal catalysed retro-Mannich reaction under the reaction conditions (Scheme 2.50).⁹⁴



Scheme 2.50. Possible synthesis of gramine derivative **278** by Mannich reaction.

However, such reaction would explain the displacement of the dimethylamino group but a retro-Mannich reaction would lead to compound **272** instead of compound **277**.

A most reasonable pathway for the gramine decomposition would be to think about a fragmentation type reaction, responsible for the displacement of the dimethyl amino group. Indeed, as proposed in scheme 2.51, the dimethyl amino group could easily bind to one of the metals in solution (palladium, copper or silver) and become activated. The electrons on the nitrogen atom of the indole could push the double bond between C(2) and C(3) out the ring system creating the unstable intermediate **287**. Eventually, any nucleophile such as traces of water or acetate could add on the exocyclic double bond affording a benzylic alcoholic species that could rapidly be oxidised to **277**.⁹⁵



Scheme 2.51. Possible formation pathway of **277** from **278**.

The same formation of **277** was observed when the 3-methylindole derivative **276** was used (table 2.2, entries 5 to 7). Once again the methyl group in allylic position has proved to be too sensitive under such oxidative reaction conditions. Anhydrous reactions carried out under argon or using degassed solvents gave the same results and in all the cases the allylic oxidation of **276** and **278** could not be avoided.

A gratifying aspect was that these allylic oxidations leading to the *in situ* generation of 3-carboxyaldehyde indoles **277** seemed to be directly followed by the oxidative cyclisation of **277** to **284**. Although isolated yields were very poor, these results were very encouraging to pursue.

A very small screening of reaction conditions was realised using the 3-carboxyaldehyde derivative **277** as starting material (table 2.2, entries 8 and 9) and medium ring cyclised product **284** could be isolated in 18% yield when the reaction was performed in DMF.

Structure of 7-membered ring product **284** was secured by X-ray crystallography data (Figure 2.6).

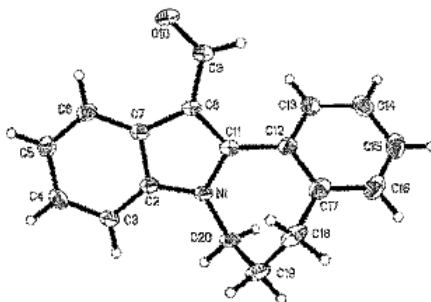


Figure 2.6. X-ray structural analysis showing the medium ring benzannulated compound **284**.

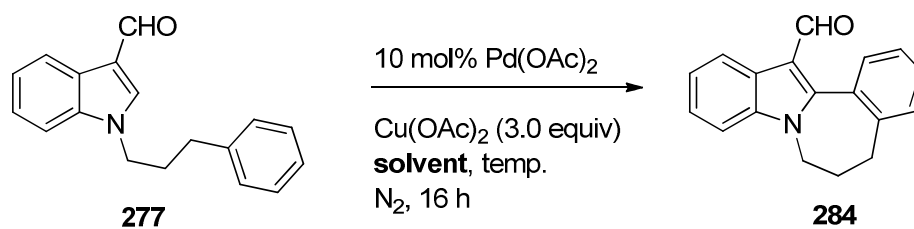
2.3.2 Optimisation of the reaction conditions

2.3.2.1 General information

Being very encouraged by these preliminary results, reaction conditions were tuned using the aldehyde derivative **277**. Solvents, base and oxidants were investigated in the first place then substrate scope was controlled in order to see if the reaction was not limited to a broad range of substrates. Later, additives, temperature, palladium loading and sources were also varied. One variable was modified at the time and reactions were monitored by LCMS and TLC. The best variable found was carried over for the next set of screening. Products were not necessarily isolated for each and every reaction and reaction efficiency was monitored by using LCMS analysis. LCMS samples were normalised before injection and the ratio between product formed and starting material left after reaction was determined using the UV signals obtained. This ratio (Pdr/SM) was used to quickly determine the best reaction conditions and not for quantification. Interesting reactions were purified by flash chromatography and yields were recorded as isolated yields.

2.3.2.2 Screening of solvents

Table 2.3. Screening of solvents.



| Entry | Solvent | °C | Product | Entry | Solvent | °C | Product |
|----------|---------------|------------|------------------|-------|---------------------------|-----|---------|
| 1 | MeCN | 80 | S.M. | 8 | <i>t</i> BuOH | 110 | traces |
| 2 | Toluene | 110 | S.M. | 9 | <i>t</i> AmOH | 110 | traces |
| 3 | Chlorobenzene | 110 | S.M. | 10 | AcOH | 80 | S.M. |
| 4 | 1,4-dioxane | 110 | traces | 11 | TFA | 80 | S.M. |
| 5 | DMF | 110 | 18% isol. | 12 | PivOH | 110 | S.M. |
| 6 | DMA | 110 | 38% isol. | 13 | DMSO | 110 | S.M. |
| 7 | NMP | 110 | 26% isol. | 14 | 1,4-Dioxane + 10% DMSO | 110 | traces |

One interesting feature was the stability of both starting material and product in the set of solvents explored. Indeed, reactions were surprisingly clean and no obvious by-products could be detected or isolated.

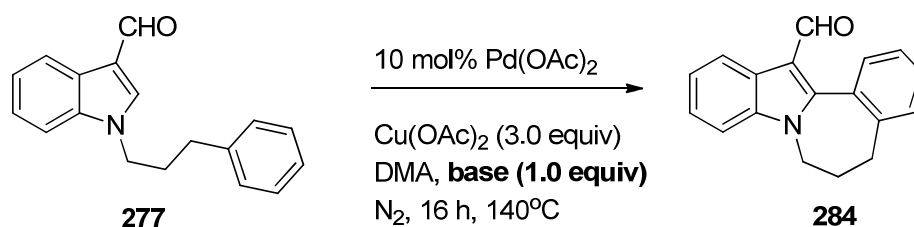
Generally, aromatic as well as low boiling point solvents did not provide any product and interestingly, the same observation was made when protic or acidic solvents were used (entries 8 to 12). This was even more surprising considering the fact that out of twelve examples of intramolecular oxidative cyclisation described in the introduction part, eleven involved acidic solvents. Indeed, depending on the substrate targeted TFA, acetic acid and pivalic acid were solvents of choice for Dong,⁴⁵ Fuji and Ohno,^{59,96} Fagnou and DeBoef.^{49,60,70}

Results obtained using polar amide types of solvents were very encouraging (entries 5 to 7). DMA gave the best result with product isolated in nearly 40%. This represents a 20% increase in yield compared to the previous experiment performed in DMF.

As the reaction studied was intramolecular, the concentration of the substrate was also investigated. Diluted systems, which tend to favour intramolecular transformations, were slower and less effective than the one carried out at higher concentration. Eventually, DMA was defined as the solvent of choice for the next screenings and the concentration of substrate was set out at 0.2M.

2.3.2.3 Screening of bases

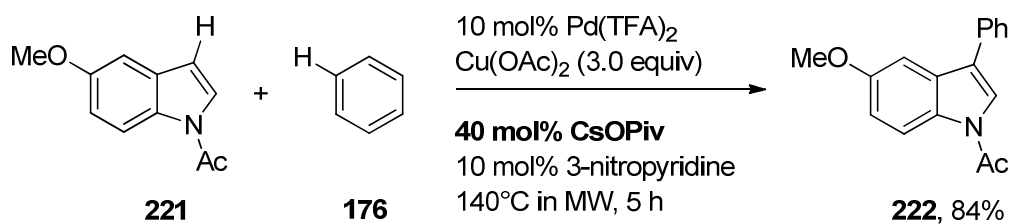
Table 2.4. Screening of bases.



| Entry | Base | Product | Entry | Base | Product |
|----------|------------------------------------|------------------|-------|---------------------------------|-----------|
| 1 | - | 38% isol. | 4 | Cs ₂ CO ₃ | 75% isol. |
| 2 | K₂CO₃ | 73% isol. | 5 | CsOPiv | <70% |
| 3 | KOAc | 70% isol. | 6 | NaOtBu | <70% |

The use of base played a key role in the efficiency of the reaction. Indeed, our system required one equivalent of carbonated or acetate type of base to be truly efficient. Other bases such as sodium *tert*-butoxide, caesium pivalate and silver salts did not give good results. Isolated yields rose up to 75% when potassium carbonate or acetate and caesium carbonate were used.

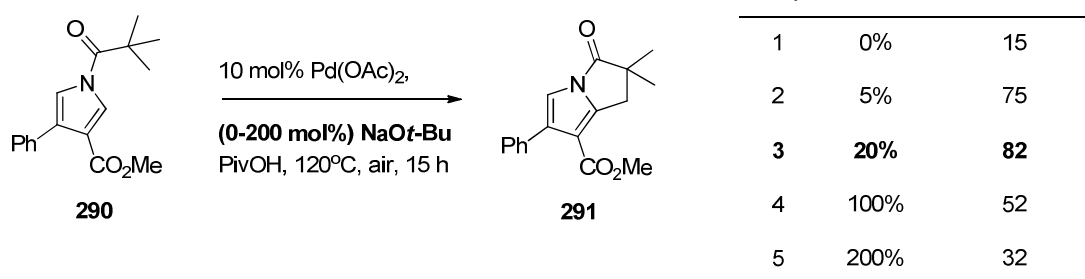
Fagnou *et al.* formerly reported that the amount of base used in oxidative cross-coupling reactions could be critical to achieve great efficiency and in some cases had to be carefully tuned. In fact, caesium pivalate used in catalytic amount increased the catalytic turnover and reproducibility of the reaction presented in scheme 2.52.⁴⁶



Scheme 2.52. Caesium pivalate an effective additive for oxidative coupling reaction.

However, the beneficial impact of the catalytic quantity of caesium pivalate used in the reaction was not perfectly clear, but the authors suggested that the base could interact with the Pd(TFA)₂ to generate palladium pivalate early in the reaction.

Sodium *tert*-butoxide was also employed in 20 mol% for the intramolecular oxidative coupling of pyrroles.⁷⁰ Experimental results presented in scheme 2.53 clearly show the importance of a fine tuning of the base loading to maximise the efficiency of the reaction. In this case, Fagnou and co-workers suggested that sodium *tert*-butoxide deprotonated the pivalic acid used as solvent to generate the pivalate anion which was believed to act as a catalytic proton shuttle from the substrate to the solvent.



Scheme 2.53. Importance of base loading in oxidative cross-coupling reaction.

As we have seen from the two previous examples, the base loading could play a crucial role in the reaction. Therefore, the amount of base required for our chemistry was also screened from 0 to 1.5 equivalents. The ratio of product formed over starting material left after reaction was plotted against the amount potassium carbonate involved in the reaction (Figure 2.7).

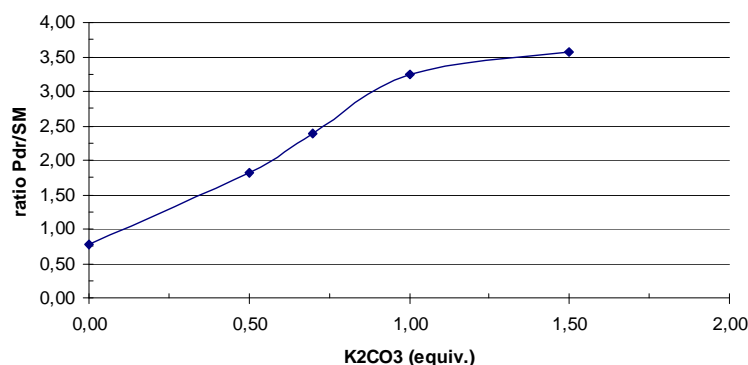


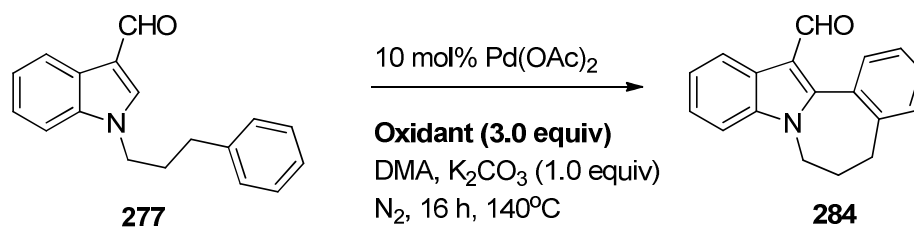
Figure 2. 7. Influence of the base on the reaction.

We noticed that the rate of formation of the products and the yields increased significantly from zero to one equivalent of base used. Above one equivalent, the excess of base added did not improve the yields dramatically. The fact that equimolar amount of base were required could suggest that the base is involved in the mechanism of the reaction perhaps *via* a base-assisted deprotonation-metalation step. This aspect of the mechanism will be discussed later in the chapter.

Considering the price of caesium carbonate (£296/500g) compared to potassium carbonate (£13/500g), we decided to use potassium carbonate instead of caesium carbonate for the next screening even if caesium carbonate offered slightly better yields (2 - 5%).

2.3.2.4 Screening of oxidants

Our next screening was focused on the oxidant. Although copper acetate has shown strong results regarding the oxidative cyclisation of **277** to **284**, a set of other oxidants has been screened in order to check if we could substitute copper acetate by a more environmental friendly oxidant.

Table 2.5. Screening of oxidants

| Entry | Oxidant | Product | Entry | Oxidant | Product |
|-------|---------------------------------|-----------|-------|--|---------|
| 1 | Cu(OAc) ₂ | 73% isol. | 8 | AgOAc | traces |
| 2 | CuCO ₃ | traces | 9 | AgF | traces |
| 3 | CuCl | S.M. | 10 | B.Q. | S.M. |
| 4 | CuCl + O ₂ | traces | 11 | K ₂ S ₂ O ₈ | decomp. |
| 5 | O ₂ (1 atm) | traces | 12 | PIDA | decomp. |
| 6 | Ag ₂ CO ₃ | traces | 13 | TBHP | S.M. |
| 7 | AgTFA | S.M. | 14 | TBP | S.M. |

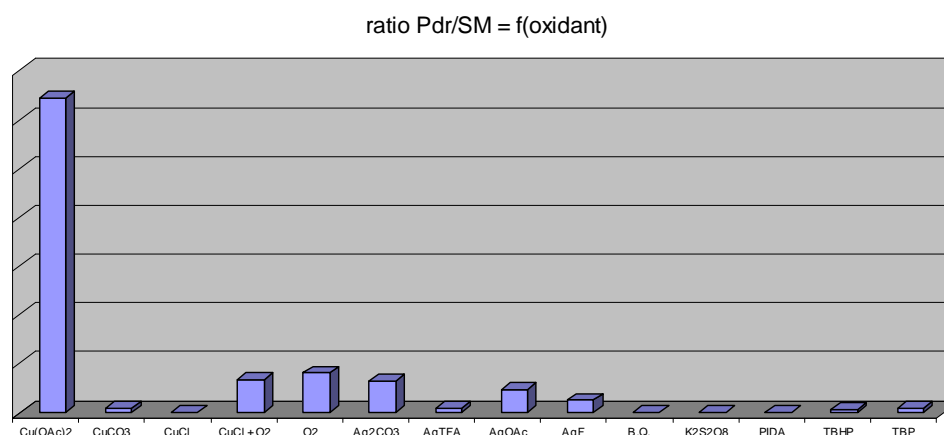
**Figure 2.8.** Visual representation of the ratio product / starting material depending on the oxidant used.

Table 2.5 and figure 2.8 represent a selection of oxidants screened and three groups can easily be distinguished. Copper salts, silver salts and organic compounds were tested and only copper acetate gave good results. Indeed, even after 48 hours, other metallic salts gave clean reaction mixtures but only trace amounts of product were observed. Potassium persulfate and organic oxidative agents such as benzoquinone,

phenyliodine bis(acetate) and peroxides failed to provide any product. Following the unsuccessful optimisation study described above, we decided to use copper acetate as oxidant in our catalytic system and the loading was also controlled. Likewise the base loading screening, the ratio of product formed over starting material left were recorded and plotted against the amount of oxidant used. (Figure 2.9).

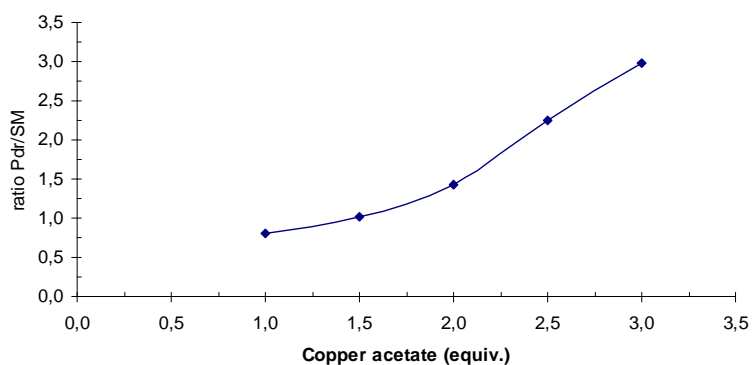


Figure 2.9. Oxidant loading monitored by LCMS.

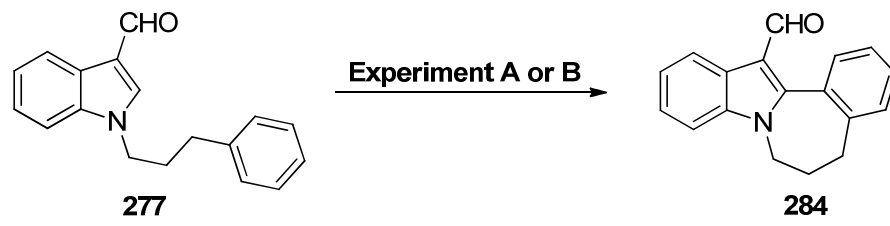
Surprisingly we found that at 140°C three equivalents of copper acetate were required for the reaction to afford good yields.

We hypothesised that under harsh reaction conditions, copper acetate could quickly get denatured and/or decomposed; therefore a large amount of copper acetate would be needed for the reaction to happen smoothly and to suppress any side reaction.

The stability of copper acetate was controlled by carrying out a set of control experiments (Table 2.6).

In experiment A, the reaction vessel was charged with all the reagents excepted $\text{Pd}(\text{OAc})_2$ and heated at 140°C for 3 hours. After heating for 3 hours, the reaction mixture, initially green, turned out to have an orange / brown colour and LCMS analysis did not indicate any starting material decomposition or product formed. Palladium acetate solubilised in DMA was injected into the vessel and the reaction was heated for 13 more hours. Surprisingly, at the end of the reaction only 16% yield of product could be isolated.

Table 2.6. Study of copper acetate stability under the reaction conditions.



277 **Experiment A or B** **284**

| Exp. | Conditions | 284 (%) |
|------|--|---------|
| A | i) Cu(OAc) ₂ (3.0 equiv), K ₂ CO ₃ (1.0 equiv), DMA, 140°C, 3 hrs. | 16 |
| | ii) Pd(OAc) ₂ (10 mol%), 140°C, 13 hrs | |
| B | i) Pd(OAc) ₂ (10 mol%), Cu(OAc) ₂ (3.0 equiv), K ₂ CO ₃ (1.0 equiv), DMA, 140°C, 5 hrs. | 74 |
| | | |

Unlike experiment A, experiment B in which all components were added together at the same time, the reaction provided the desired product in 74% yield.

Experiment A indicated that under these reaction conditions copper acetate degraded very quickly and in less than 3 hours, copper acetate almost lost its complete activity. It is difficult to get a real explanation of this phenomenon but this could probably be due to either a ligand exchange on the copper which made it inactive or by a change in its oxidation state which would explain the change in colour during the reaction.

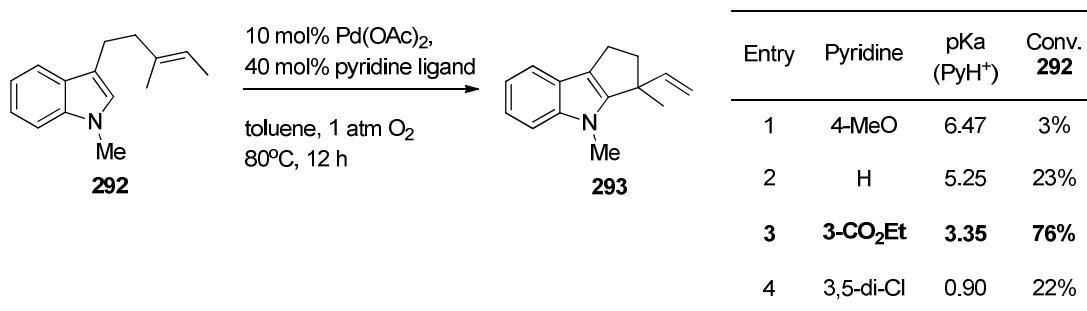
Considering these results, the reaction temperature was decreased below 100°C and cyclised product was eventually obtained in 77% yield when the reaction was carried out at 90°C. Although this represented our best result so far, three equivalents of copper acetate were still required to achieve the transformation.

2.3.2.5 Fine tuning of the reaction conditions

Chemists have formerly showed that additives could be used stoichiometrically or catalytically in oxidative coupling reactions to stabilise the palladium species and thus obtained better yields.

The most relevant example regarding the use of additive in oxidative coupling reaction was probably reported by Fagnou and co-workers in 2007.⁴⁶ In this paper, the authors successfully managed to selectively couple unactivated arenes with indoles *via* double C-H bond activation. 3-nitropyridine was used catalytically as an additive and proved to be vital to achieve superior turnover numbers and reproducibility (Scheme 2.52). The authors suggested that the pyridine additive could stabilise the palladium(0) species before re-oxidation and therefore prevented the formation of palladium black.⁴⁶

Stoltz and Ferreira also reported the importance of the electronics of pyridine additives on oxidative indole annulation reactions.⁹⁷ A range of electron-rich, -neutral and -poor pyridines have been tested and the authors evaluated the strong relationship between the binding affinity of pyridines with palladium and the reactivity observed. Electron-rich pyridines affording less electrophilic Pd-pyridine systems failed to provide good yields whereas electron deficient pyridines such as ethyl nicotinate exalted the electrophilic aspect of the catalyst making it more reactive (Scheme 2.54). However, very electron-poor ligands were unable to sufficiently bind to palladium, thus hampering both reactivity and palladium re-oxidation.

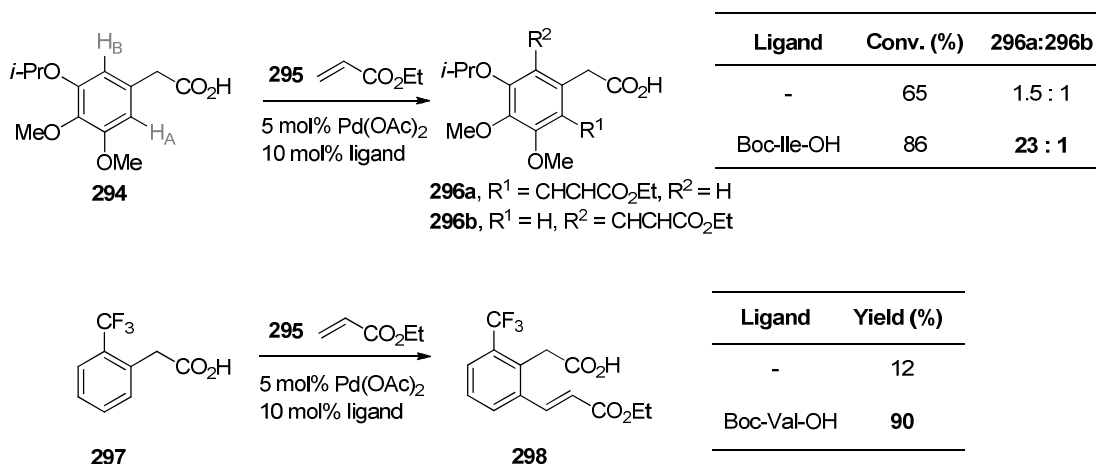


Scheme 2.54. Pyridine ligands mediated oxidative annulations of indoles.

Yu *et al.* also showed that catalytic 2,6-dialkylpyridine ligand proved to be excellent additives for the *meta*-selective olefination of highly electron-deficient arenes.⁹⁸

Amino acid derivatives as additives in C-H olefination have also been studied by the Yu's group.⁹⁹ Selectivity in the transformation was achieved by modulating the steric

properties of the metal centre through the coordination of chiral *N*-protected amino acids and the isomeric distribution depended on the structure of the amino acid side chain used (Scheme 2.55).



Scheme 2.55. *N*-protected amino acids enhanced reactivity and selectivity of C-H olefination reactions.⁹⁹

Considering the observations made by Fagnou *et al.* regarding the oxidative coupling of arene – arene and by Stoltz *et al.* and Yu *et al.* about C-H olefination reactions, we decided to carry out a screening of additives to find out if we could enhance the yields even more (Table 2.7).

Table 2.7. Screening of additives

| Entry | Additive | Pdr/SM | Entry | Additive | Pdr/SM |
|-------|--------------------------------------|------------|-------|-----------------------------------|--------|
| 1 | No additive | 3.23 (73%) | 7 | 3-CN Py (pKa = 1.45) | 3.20 |
| 2 | DMAP (pKa = 9.56) | 3.20 | 8 | 3-NO ₂ Py (pKa = 0.81) | 3.37 |
| 3 | 2,6-lutidine (pKa = 6.77) | 3.37 | 9 | 2,2'-bipyridyl | 0.32 |
| 4 | 4-OMe Py (pKa = 6.47) | 3.20 | 10 | 1,10-phenanthroline | 0.19 |
| 5 | Py (pKa = 5.29) | 3.37 | 11 | Boc-val-OH | 1.25 |
| 6 | 3-CO ₂ Et Py (pKa = 3.35) | 3.37 | 12 | Boc-Ile-OH | 1.32 |

Reaction conditions: compound **277** (0.2 mmol), 10 mol% Pd(OAc)₂, 20 mol% additive, Cu(OAc)₂ (3.0 equiv.), K₂CO₃ (1.0 equiv.) in DMA 0.2 M at 90°C for 24 h.

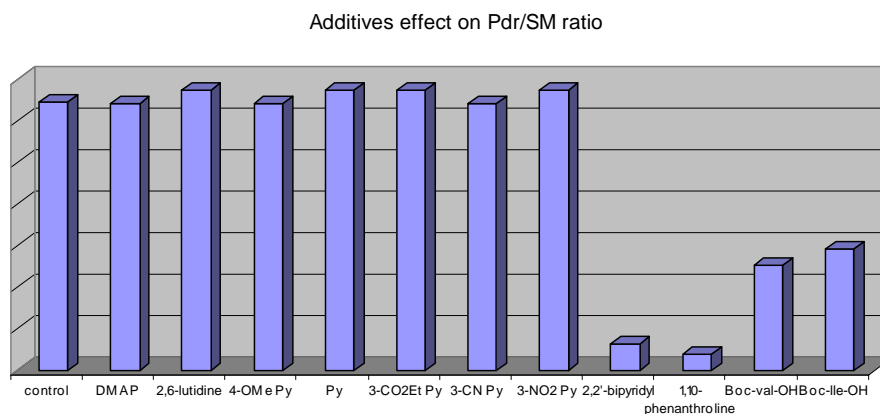


Figure 2.10. Observed Pdr/SM ratio depending on the additives used

Bulky, electron-rich and electron-deficient pyridine derivatives did not improve the yield of the reaction. Indeed, no large differences were observed between them and yields were estimated to be 10% greater or lower than the control experiment which did not contain any additive. By repeating these experiments, these small fluctuations were found to be due to experimental errors and no obvious relations with the ligands were observed. Even the 3-nitropyridine ligand formerly used by Fagnou and co-workers failed to increase the yield. Two bidentate pyridine ligands (entries 9 and 10) were tested but products were obtained in far lower yields. This could be due to the strong coordinating properties of 2,2'-bipyridyl and 1,10-phenanthroline compounds, which could bind tightly to the palladium decreasing its reactivity or to the copper hampering the re-oxidation of the catalyst. Eventually, two protected amino acids were screened and proved to be worse. It is also worth to mention that no side-reactions between ligands and substrate were observed while using such pyridine or amino acid derivatives, which once again showed the good orthogonal behaviour of the reaction.

A very brief screening of 4 different palladium(II) catalysts has been carried out. Pd(OAc)₂ and PdCl₂ showed the same reactivity and conversion up to 75% were successfully achieved with compound **277** whereas Pd(acac)₂ and Hermann-Beller catalyst provided lower conversions. From this small study, it is quite difficult to find

an explanation about the reactivity of the catalyst and a larger screening would have to be performed to get more information.

2.3.2.6 Optimised reaction conditions

We successfully managed to carry out the first oxidative cyclisation reaction of medium rings by palladium catalysis. DMA was selected as best solvent to achieve the transformation. Palladium loadings were screened along with oxidant and it was found that 10 mol% of palladium acetate and stoichiometric amount of copper acetate as oxidant were required for the reaction. Base, such as potassium carbonate, was also crucial to achieve good starting material conversion whereas additives were not necessary. At last, temperature has proven to be a vital parameter and excellent results were obtained at 90°C.

Best reaction conditions were defined as: 10 mol% Pd(OAc)₂, Cu(OAc)₂ (3.0 equiv.), K₂CO₃ (1.0 equiv.) in DMA 0.2M at 90 °C.

Using these conditions, 7-membered ring aldehyde derivative **284** was isolated in nearly 80% yield. However, despite the fact that a good starting material conversion was obtained for the aldehyde derivative, the reaction failed to provide any product with other substrates. To ensure that the reaction was not limited to a small set of compounds, a substrate scope study was carried out. This study will be presented and discussed in the following section.

2.3.3 Substrate Scope

With our optimised reaction conditions in hand, we investigated the substrate scope of the reaction. This aspect of the project is very important as it shows the direct applicability of the methodology developed.

Our substrate choice allowed variations at four different sites on the molecule (Figure 2.11). Indeed, the substitution pattern or the length of the tethering chain (**A**) could easily be changed. Diverse functional groups could be introduced at the position C(3) of the indole (**B**) or could also be added on the indole scaffold (**C**). Eventually, the terminal tethered aromatic moiety could also be modulated (**D**).

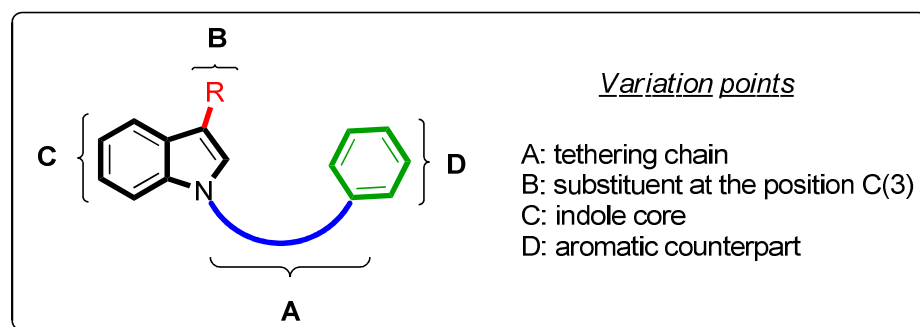


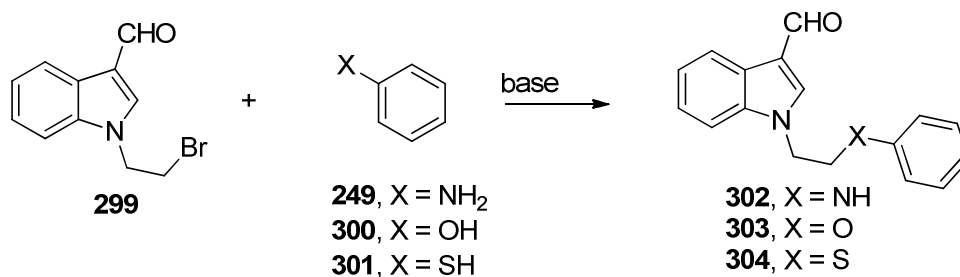
Figure 2.11. Four modification sites of the starting material.

2.3.3.1 7-membered ring systems

2.3.3.1.1 Tethering chain modifications

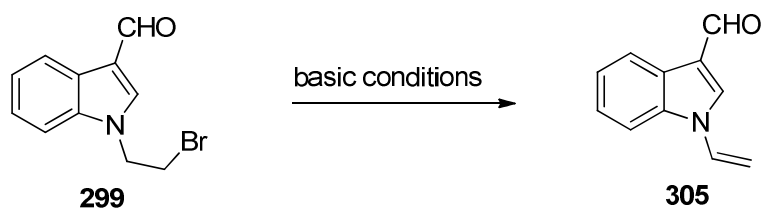
The first section will be focused on the modification made on the side chain of the starting materials and the formation of 7-membered and smaller ring systems will only be discussed. Work regarding the synthesis of bigger ring systems than 7-membered will be described later in the thesis.

Aliphatic chains initially used as tethers were modified and substituted with heteroatoms. We thought that an easy way to prepare compounds **302** - **304** was to treat the readily prepared bromoindole compound **299** with commercially available nucleophiles such as phenols, anilines, thiophenols in a presence of a base (Scheme 2.56).



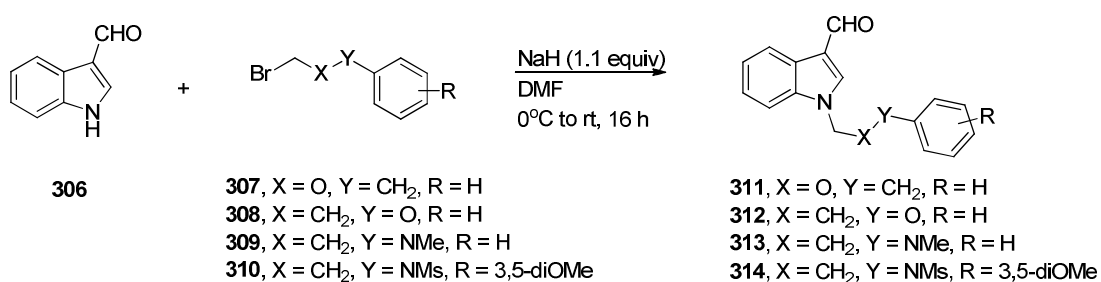
Scheme 2.56. Ideal synthetic route for starting materials preparation.

However, under basic conditions, starting material **299** decomposed and eliminated bromine to give the alkene compound **305**. Typical synthetic procedure involving sodium hydride in DMF,⁸⁸ or potassium carbonate in refluxing 2-butanol,¹⁰⁰ or sodium hydroxide and tetrabutylammonium bromide as phase transfer catalyst in water / toluene biphasic solvents¹⁰¹ failed to provide the desired product and gave compound **305** instead (Scheme 2.57).



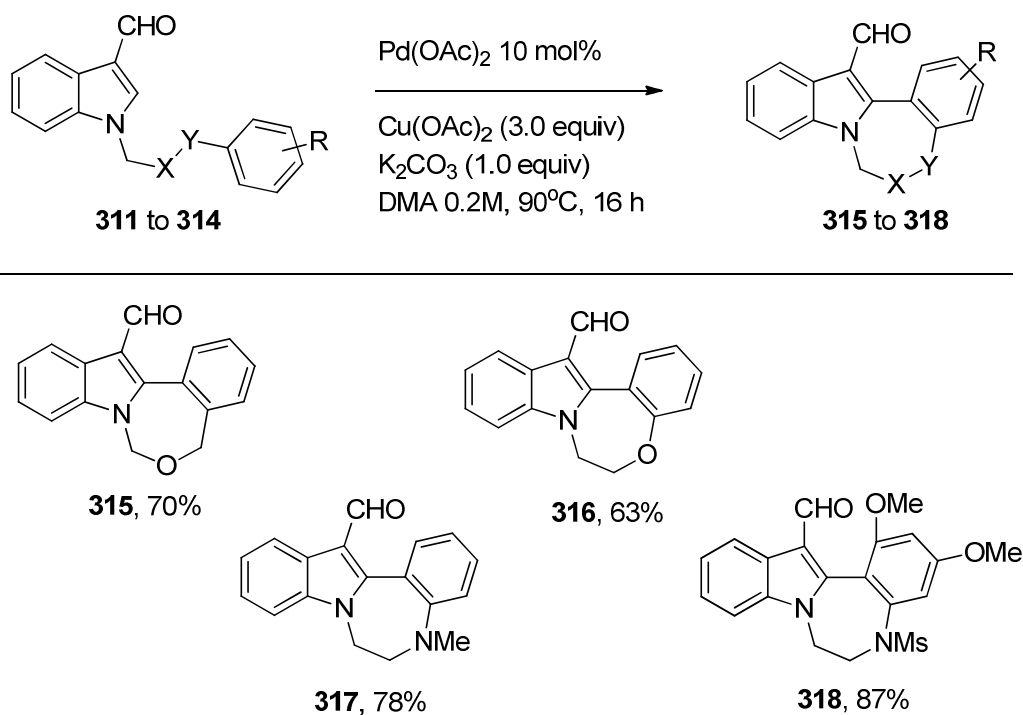
Scheme 2.57. Decomposition of the starting material **299**.

We then decided to synthesise the starting materials (**311** - **314**) by alkylating the indole 3-carboxyaldehyde **306** with various alkyl halides (Scheme 2.58).



Scheme 2.58. Synthesis of starting material with functionalities on the tethering chain.

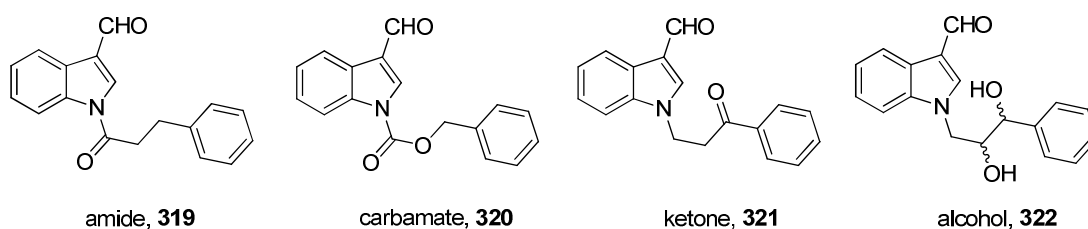
Functional groups such as benzyl ether, *N*-methyl and *N*-mesylate groups were successfully introduced on the tethering chain and starting materials reactivity was examined under our optimised oxidative coupling reaction conditions. 7-membered ring products obtained after reaction are presented below in scheme 2.59.



Scheme 2.59. Oxidative ring closure reaction providing substituted 7-membered ring systems.

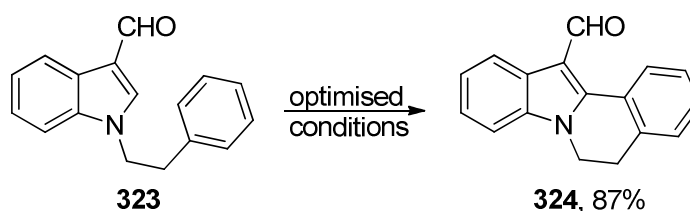
Gratifyingly, the catalytic system previously set out permitted to produce 7-membered ring system containing heteroatoms and oxazapane derivatives **315** and **316** as well as diazapane analogues **317** (NMe) and **318** (NMs) were isolated in good yields. Interestingly, no five-membered ring product from C-H activation at the benzylic position was observed for substrate **311**, despite the susceptibility of benzyl ethers to oxidation.¹⁰² sp^2 C-H bond activation to form the medium ring was evidently favoured under our reaction conditions. Moreover substrates containing electron-rich aromatic rings such as dimethoxy groups **314** were also very well tolerated.

However, starting materials containing unsaturated functional groups such as amide **319**, carbamate **320** and ketone **321** were unstable under these reaction conditions. Substrate having free alcohol groups on the tethering chain **322** presented also the same sensitivity and under reaction conditions all starting materials were hydrolysed to the free 1H-indole 3-carboxyaldehyde **306**. This could certainly be explained by the fact that such functional groups were labile and easily cleavable under basic and oxidative conditions.



Scheme 2.60. Unstable starting materials under the reaction conditions.

The length of the tethering chain has been varied and a smaller ring has been prepared. Because our main focus was not the formation of small ring systems only one annulated six-membered ring compound has been synthesised to prove that such class of substrates could easily be made using our chemistry. In fact, the reaction proved to be very efficient and product **324** was isolated in nearly 90% yield (Scheme 2.61).



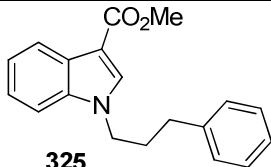
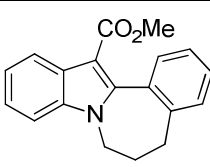
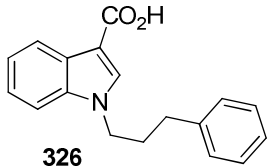
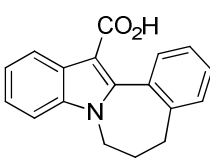
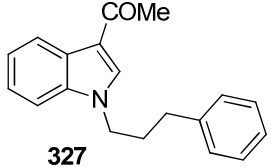
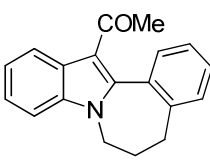
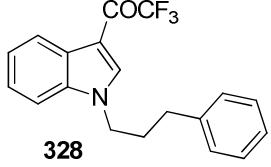
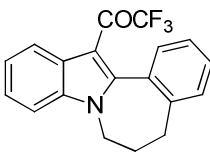
Scheme 2.61. Formation of annulated 6-membered ring using our reaction conditions.

2.3.3.1.2 Functional group modifications at the C(3) position of indole

As we noticed previously the oxidative cyclisation of indoles without substituents at the position C(3) proved to be unsuccessful. It also appeared from the screening of the reaction conditions that the functional group at C(3) must be carefully chosen. An

aldehyde promoted the reaction whereas methyl and CH_2NMe_2 failed to provide any product. Considering the success of the aldehyde group at C(3), we decided to investigate the feasibility of the reaction using other carbonyl groups such as $-\text{CO}_2\text{Me}$, $-\text{CO}_2\text{H}$, $-\text{COMe}$ and $-\text{COCF}_3$ (Table 2.8).

Table 2.8. Expected products from oxidative coupling of 3-carboxyalkyl indole starting materials

| Entry | S.M. | Product | Yields (%) |
|-------|---|--|------------|
| 1 |  <p>325</p> |  <p>329, 24%</p> | |
| 2 |  <p>326</p> |  <p>330, decomp.</p> | |
| 3 |  <p>327</p> |  <p>331, < 10%</p> | |
| 4 |  <p>328</p> |  <p>332, < 10%</p> | |

Disappointingly, none of the expected products could be isolated in good yields. Indole starting material **326** bearing a carboxylic acid function at the position C(3) decomposed under the reaction conditions and LCMS analysis of the crude mixture showed significant amount of decarboxylated product formed along with other side-reactions. The loss of carboxylic acid functional group on the starting material **326** could be rationalised by a palladium catalysed decarboxylative side-reaction. Cyclised ester derivative **329** could be isolated in 24% yield and a small screening of reaction conditions was carried out in order to raise the yield but all attempts failed to

do so. Surprisingly, ketone derivatives **327** and **328** were poor substrates for the reaction and respective products could only be detected by LCMS analysis in very small quantity. Electronic and steric factors of both 3-formyl- **277** and 3-acetylintole derivatives **327** were compared in order to understand and rationalise their difference in reactivity.

Extensive work carried out by Andonovski and Stojkovic on pK_a determination of 3-carboxyalkyl indoles have shown that pK_a s of protonated 3-formylindole (FIH^+) and 3-acetylintole (AIH^+) were very close with respective values of -1.7 and -1.4.¹⁰³⁻¹⁰⁵ pK_a of protonated indole (IH^+) was also determined and presented a value of -3.6. An obvious observation made by the authors was that both aldehyde and acetyl groups placed at the position C(3) had an strong electronic impact on the indole. Indeed, protonated indole (IH^+) appeared to be more acidic than the two other protonated species AIH^+ and FIH^+ . Another interesting aspect was that both carbonyl groups seemed to have the same electronic trends as both pK_a values obtained were almost identical ($pK_{aCHO} = -1.7$ and $pK_{aCOMe} = -1.4$).

Considering these observations, we could probably assume that both starting materials prepared, 3-formyl- and 3-acetylintole derivatives **277** and **327**, have similar electronics. Therefore the disparity in reactivity between these two starting materials could probably be explained by a difference in sterics rather than by a difference in electronics. It is not clear yet why the results obtained were so different but another possible explanation would be that the carbonyl group acts as a directing group and a modification of it may result in a critical change of the spatial conformation of the substrate.

3-Fluoro- and 3-(trifluoromethyl)indole derivatives were considered to study the importance of having an electron-withdrawing group at the position C(3) without any directing effect (Figure 2.12).

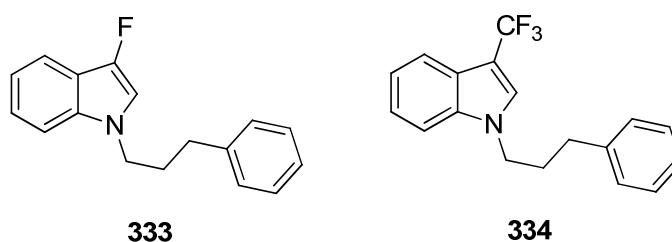
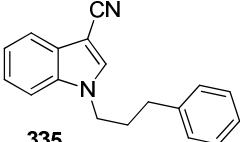
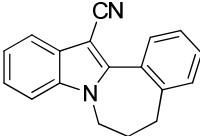
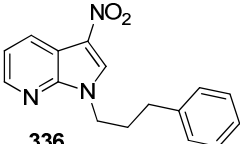
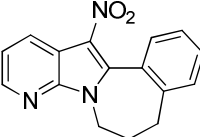


Figure 2.12. Non directing and electron-withdrawing starting materials.

However, 3-halogenoindole derivatives and particularly 3-fluoroindoles were known to be thermally unstable even at room temperature.¹⁰⁶ Moreover, the route to make the CF₃ derivative **334** proved to be long and not reliable¹⁰⁷ therefore none of them have been prepared and more robust substrates were prepared instead.

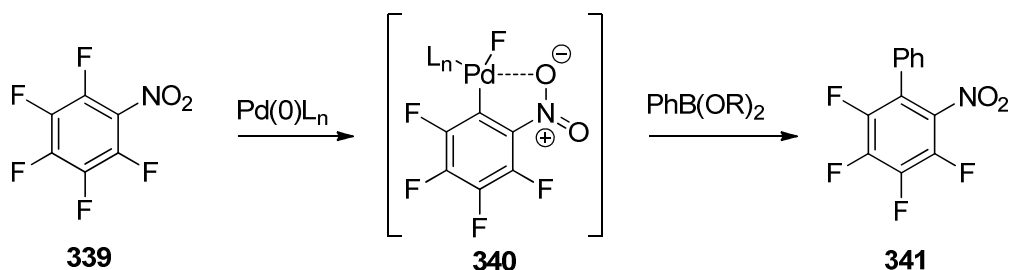
Table 2.9. Products containing cyano and nitro groups at the position C(3).

| Entry | S.M. | Product | Yields (%) |
|-------|---|--|------------|
| 1 |  335 |  337 , 79% | |
| 2 |  336 |  338 , 95% | |

Gratifyingly, powerful electron withdrawing group such as cyano and nitro proved to be excellent partners with the cyano product obtained in 79% yield and the nitro product obtained in almost quantitative yield. These two functional groups are best-known for their strong electron-withdrawing character but we could not exclude the fact that these two groups and more particularly the nitro group could also be considered as directing group.

Indeed, Kim and Yu,¹⁰⁸ Widdowson and Wilhelm,¹⁰⁹ and more recently Sandford *et al.*¹¹⁰ reported the palladium catalysed C-F activation and functionalisation of several mono- and polyfluorinated nitrobenzene derivatives under standard Suzuki-Miyaura and Stille coupling conditions (Scheme 2.62). The three groups suggested that the

nitro group, in addition to its activating electron-withdrawing properties, directed the palladium catalyst into the adjacent ortho C-F bond, thereby lowering the activation energy for the oxidative addition step. Eventually, Sanford *et al.* managed to crystallise the intermediate **340** to secure the regio-selectivity of the reaction.

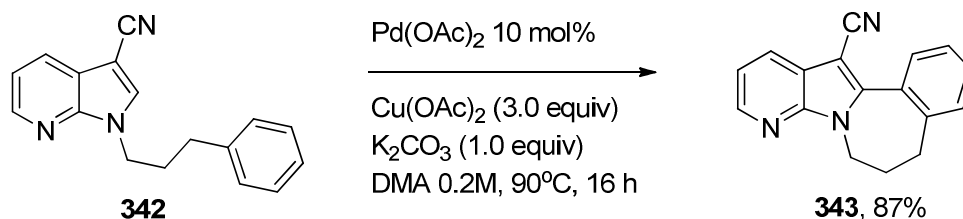


Scheme 2.62. Palladium catalysed Suzuki coupling of pentafluoronitrobenzene **339**.¹¹⁰

As reported above, the reaction required a good electron-withdrawing group at the C(3) position. Formyl-, cyano- and nitro-substrates afforded 7-membered medium ring systems in good to excellent yield. However, substrates bearing ketones, esters and acid functional groups were poor contestants for the reaction. It is unclear yet, if steric effects, spatial configuration or directing effect of the group at C(3) were involved in this failure.

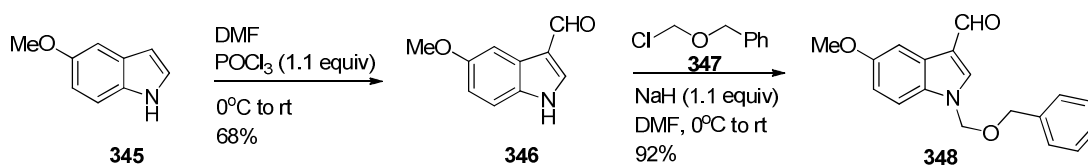
2.3.3.1.3 Modification of the indole core of the starting materials

The nitro-substrate **336**, priorly discussed proved to be an excellent partner for the reaction and it is worth noting that this compound contained a slightly different indole core than the one previously used. Indeed, 7-azaindoles appeared to be excellent structures for oxidative ring closure reaction with nitro-azaindole **338** previously isolated in 95% and novel cyano-azaindole **343** obtained in 87% yield (Scheme 2.63).



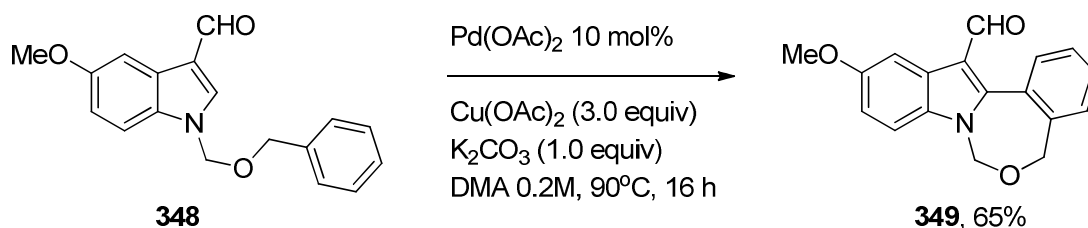
Scheme 2.63. Palladium catalysed oxidative cyclisation of 7-azaindole derivatives.

Considering the success of the cyclisation of nitrogenated substrates, the oxygenated starting material **348** was prepared. Vilsmeier-Haack reaction on 5-methoxyindole **345** afforded the aldehyde intermediate **346** in 68% yield,¹¹¹ which was then alkylated with commercial available starting material **347** to give the desired product **348** in 62% overall yield (Scheme 2.64).



Scheme 2.64. Synthesis of the oxygenated starting material **348**.

Substrate **348** was exposed to our optimised oxidative reaction conditions and afforded the desired product **349** in 65% yield (Scheme 2.65).



Scheme 2.65. Palladium catalysed oxidative coupling of oxygenated starting materials.

2.3.3.1.4 Substituted benzenes containing a tethering chain

Electron withdrawing and donating groups were tested and good functional group tolerance was also observed (Table 2.10). *para*-Substituted benzene starting materials afforded two equivalent C-H activation site whereas unsymmetrical substrate **352** with a fluorine substituent positioned at the *meta*-position presented two different sites for C-H bond activation. Indeed, *para*-compounds cyclised without ambiguity affording trifluoromethyl (CF₃) and methoxy (OMe) products in respectively 80 and 60%. However, *meta*-fluoro starting material **352** gave two separable products **355a** and **355b** in a 4:1 isomeric ratio. Assignments of the two conformers were determined by NMR spectroscopy and X-ray crystallography data of the major isomer **355a** were obtained (Figure 2.14).

Table 2.10. Oxidative cyclisation of substrates containing electron-rich and -poor tethered benzenes.

| Entry | S.M. | Product | Yield (%) |
|-------|------|---------|-------------------|
| 1 | | | 60 |
| 2 | | | 80 |
| 3 | | | 63 |
| | | | 355a : 355b = 4:1 |

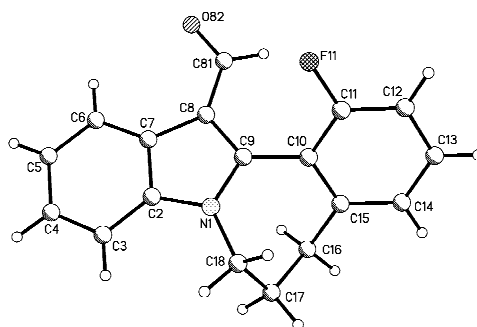
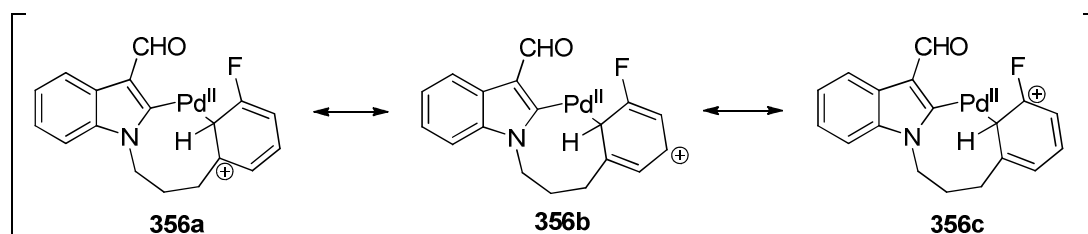


Figure 2.13. X-ray structural analysis showing major isomer **355a**.

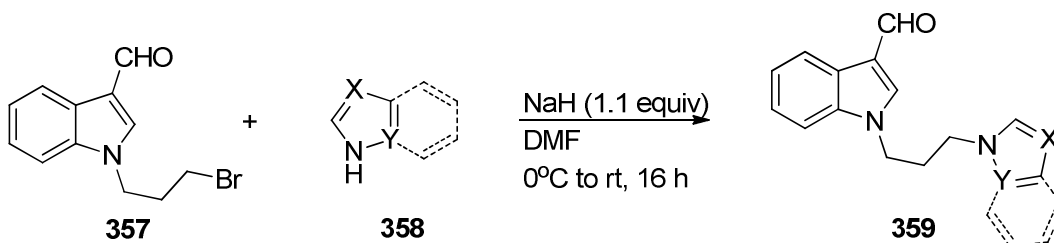
Observations obtained for *meta*-fluoro substrate **352** provided important information regarding the mechanism of the second palladation step. Indeed, such a disparity between the two C-H bonds available for cyclisation indicated that the breaking of the most activated and therefore most acidic bond (C-H_a) could be in favour of a C-H activation mechanism rather than an aromatic electrophilic substitution mechanism. Moreover, fluorine substituted arene tended to disfavour S_EAr mechanism as the positive charge created in the Wheland intermediate would be destabilised by the presence of strong electron-withdrawing group such as fluorine atom (scheme 2.66).



Scheme 2.66. Mesomeric forms of the palladacycle created by a S_EAr mechanism.

2.3.3.1.5 Heterocycle containing tethering chain

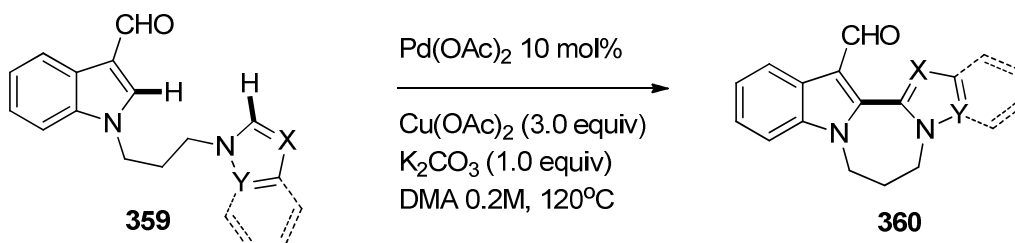
We extended the work to encompass heteroaromatic ring systems, with the aim of synthesising novel heterobiaryls annulated in a 7-membered ring. Starting materials **359** were prepared as usual by alkylation reaction of nitrogen containing heterocycles with the stable bromo-indole derivative **357** (Scheme 2.67).

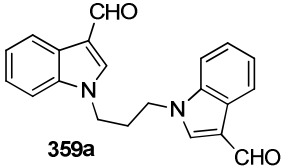
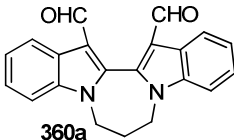
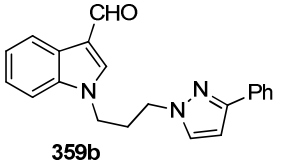
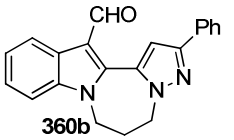
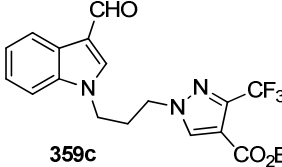
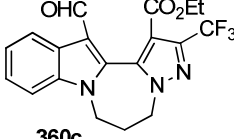
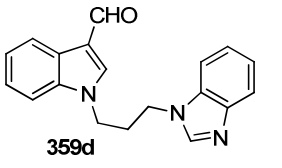
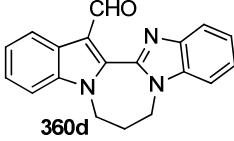


Scheme 2.67. General synthesis of indoles starting materials containing heterocycle tethering chain.

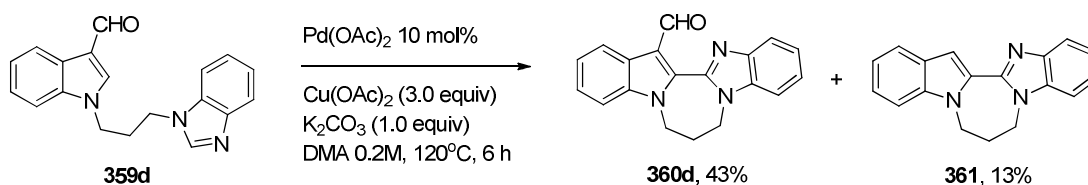
As we can see in table 2.11, the reaction was very effective for the synthesis of the bisindole **360a**, synthesised from C(2) oxidative coupling of the symmetrical precursor. Reaction conditions were a little bit different from the one previously used for the dehydrogenative coupling of indoles with arenes. The oxidative coupling of heterobiaryls required higher reaction temperature and reactions were completed in less than 8 hrs. Pyrazoles were also good substrates for the reaction with compound **360b** isolated in 84% yield. Sterically hindered and electronically poor pyrazole **360c** could also be obtained in modest yield after longer reaction time.

Table 2.11. Palladium catalysed formation of annulated 7-membered heterobiaryls.



| Entry | S.M. | °C | Time (h) | Product | Yields (%) |
|-------|---|-----|----------|--|------------|
| 1 |  359a | 120 | 8 |  360a | 91 |
| 2 |  359b | 120 | 8 |  360b | 84 |
| 3 |  359c | 120 | 24 |  360c | 43 |
| 4 |  359d | 140 | 3 |  360d | 62 |

Benzimidazole derivative **359d** reacted very quickly and newly product formed **360d** was found to undergo further decarbonylation reaction when the reaction was kept for too long (Scheme 2.68).



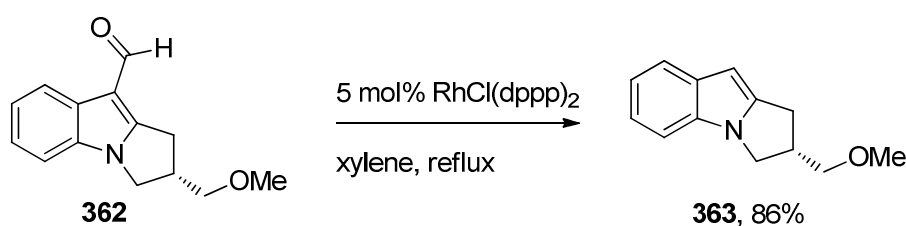
Scheme 2.68. Oxidative cyclisation and decarbonylation reaction of the benzimidazole derivative.

Interestingly, trace amounts of decarbonylated products were also detected by LCMS analysis when pyrazole derivatives were used.

The fact that no decarbonylated products were found using the previous substrates indicated that the second nitrogen atom of the benzimidazole and pyrazole scaffolds had a direct effect on the decarbonylation reaction.

Decarbonylation reaction of aryl compounds have been widely reported using rhodium (I) catalyst such as Wilkinson's catalyst $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$.¹¹²⁻¹¹⁴ Rhodium(I) complexes undergo oxidative addition with aldehydes to produce acyl rhodium(III) hydride intermediates, followed by intramolecular hydrogen transfer affording decarbonylated products.

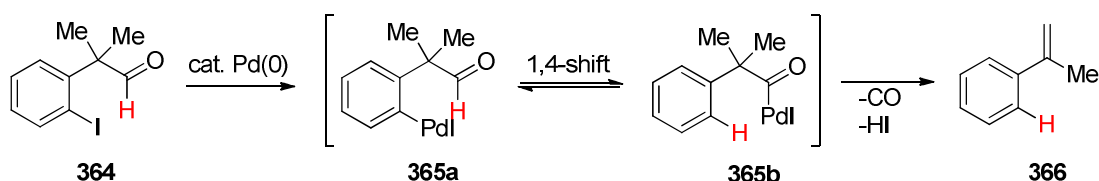
Rhodium catalysed decarbonylation of 2-carboxy- and 3-carboxyaldehyde indoles have been described by Meyer and Kruse in 1984¹¹⁵ and Bergman *et al.* in 2006 (Scheme 2.69).¹¹⁶



Scheme 2.69. Rhodium catalysed decarbonylation of 3-carboxyaldehyde indole **362**.¹¹⁶

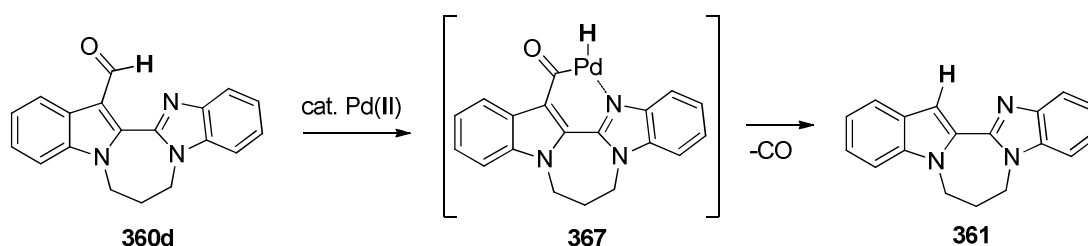
Although this reaction has been well described using rhodium (I) catalyst, palladium catalysed decarboxylation reactions of (hetero)arenes are less abundant. Larock and co-workers have reported the acyl C-H bond activation via aryl and alkyl migration of palladium to acyl.¹¹⁷

After oxidative addition of the aryl iodide **364** to palladium (0), the resulting intermediate **365a** could insert palladium (II) into the neighbouring acyl C-H bond via 1,4-shift to form **365b**. In the absence of a nucleophile, the acylpalladium intermediate **365b** underwent decarbonylation, followed by β -hydride elimination, to give the corresponding styrene derivative **366** (Scheme 2.70).



Scheme 2.70. Palladium catalysed acyl C-H activation *via* catalyst migration.

In our chemistry, we hypothesised that the oxidative cyclisation of the carbonyl group of the indole and the benzimidazole structure were brought in close proximity after oxidative cyclisation. Then the palladium (II) species stabilised by the chelating nitrogen atom of the benzimidazole could insert into the acyl C-H bond affording the acyl palladium intermediate **367**, which could rapidly undergo intramolecular proton transfer giving the decarbonylated product **361** (Scheme 2.71).



Scheme 2.71. Proposed decarbonylation pathway of the substrate **360d**.

Considering the success of the formation of 7-membered ring systems by dehydrogenative cyclisation of indoles based molecules, we attempted to extend our methodology to other heterocycles than indoles.

2.3.3.1.6 Oxidative cyclisation of nitrogenated heterocycles.

C-H activation and functionalisation of benzimidazole and purine derivatives under our reaction conditions were investigated by myself while Donald McAusland (first year PhD student at that time in our group) investigated the cyclisation of pyrroles.

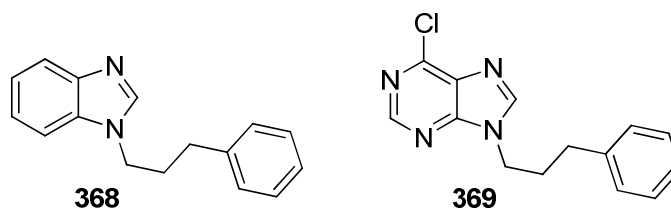


Figure 2.14. Benzimidazole and purine derivatives tested.

Benzimidazole linked with indole previously gave satisfying results, however when benzimidazole was tethered with a benzene ring no reaction happened. Reaction

conditions have been modified to get the reaction to work but starting material **368** was unreactive and recovered at the end of the reaction.

At the same time, purine derivative **369** was subjected to cyclisation but also failed to provide any desired product. In most of the reaction conditions tried, starting material was recovered but in some cases labile chlorine atoms was found to be removed from the substrate.

Pyrroles were found to be quite unstable under such oxidative conditions and only traces amounts of the product could be detected by LCMS analysis.

2.3.3.1.7 Conclusion on the substrate scope of the reaction

Indoles tethered with (hetero)arenes were found to be versatile substrates for the formation of 7-membered annulated ring systems by oxidative coupling. Indeed, four different sites could easily and rapidly be modified on the starting material, affording a wide panel of interesting molecules. A large variety of medium rings have been synthesised and the chemistry has good functional group tolerance. However, functional groups such as amides, ketones and alcohols, presenting labile properties, were unstable under the reaction conditions. Eventually, the transformation also proved to be efficient for the formation of novel heterobiaryl medium ring systems such as bisindole, indole-benzimidazole and indole-pyrazole. Attempts to substitute the indole core by another heterocycle failed to produce any cyclised product.

2.3.3.2 Larger ring systems

Considering the success of annulated 7-membered indole ring systems, we decided to use the established methodology for the synthesis of larger medium rings and 8-membered cycles were mainly targeted.

Starting materials were prepared by extending the tethering chain with one extra carbon atom (Figure 2.15). Substrate **370** was firstly tested but failed to product any cyclised product in isolatable amount. Indeed, LCMS analysis showed a signal having the mass of the expected product, but the yield associated to that peak was probably inferior to 5%.

As we have shown before, 3-nitro-substituted indole and bisindole derivatives were excellent substrates for the reaction, with products isolated in 95 and 91% yield respectively. Therefore, analogues **371** and **372** were synthesised but proved to be completely unreactive.

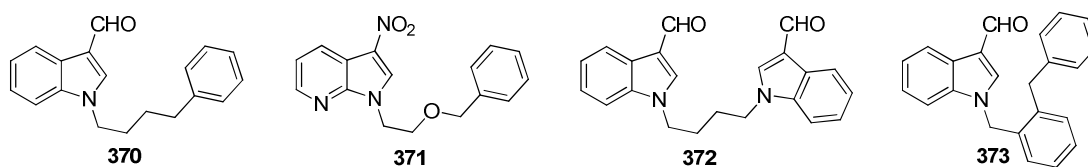
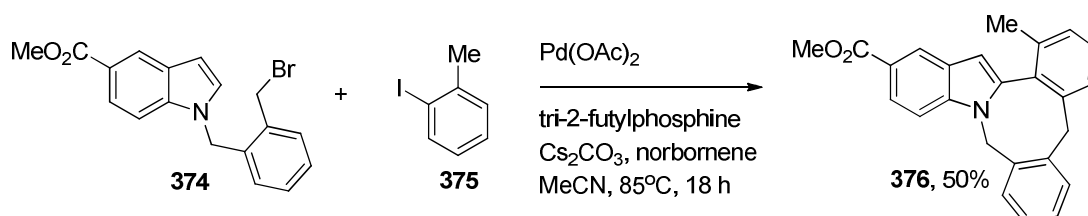


Figure 2.15. Starting materials prepared for 8-membered rings formation.

These observations suggested that a specific spatial conformation, with the second partner for C-H activation pointing far from the C(2)-palladated indole species was probably responsible for the failure of the reaction. To solve this problem, we envisaged to synthesise a starting material, which would have a different conformation from the ones previously prepared. Promisingly, Lautens and co-workers reported a norbornene-mediated palladium catalysed synthesis of very interesting pentacyclic benzofused indole structures containing 8-membered rings (Scheme 2.72).^{118,119}

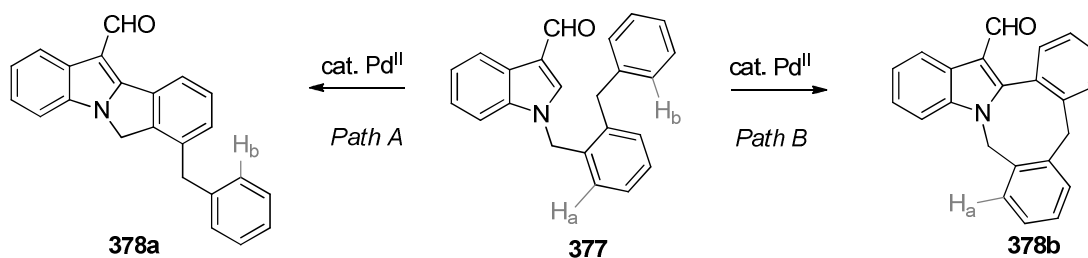


Scheme 2.72. Norbornene-mediated palladium catalysed synthesis of 8-membered rings.

Thus, this encouraged us to design a starting material **373** that could lead to the formation of the same kind of structure prepared by Lautens *et al.*.

Substrate **373** was also an interesting compound to work with because two different C-H bonds were available for cyclisation. Indeed, 5- and 8-membered rings **378a** and **378b** could be obtained depending if either C-H_a or C-H_b was activated (Scheme 2.73). Unfortunately limiting the degrees of freedom the alkyl chain did not improve

the reactivity of the reaction towards the formation of eight-membered rings and none of the expected product could be detected.

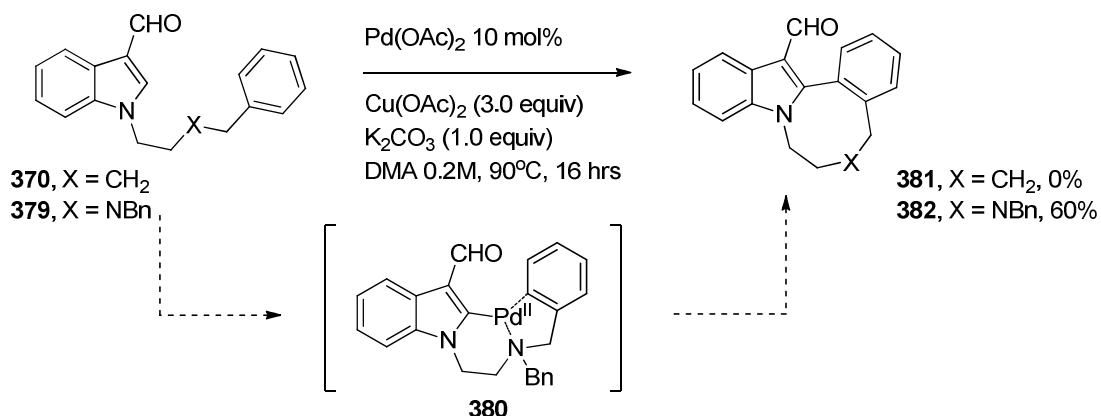


Scheme 2.73. Two possible cyclisation pathways for reaction involving substrate **377**.

It was also very surprising to notice that 5-membered compound **378a** was not obtained. This could possibly be due to steric interactions that could push the C-H_a bond away from the palladium centre.

After a disappointing start trying to synthesise 8-membered rings *via* double C-H activation, we reasoned that the replacement of a methylene in the tethering chain with a heteroatom might serve to both reduce transannular strain as well as providing a stabilising interaction with the presumed Pd(II) intermediate in the reaction.¹²⁰

We were pleased to notice that incorporation of a dibenzylamine group **379** into the substrate proved a success, providing 8-membered diazocane derivative **382** in 60% yield (Scheme 2.74).



Scheme 2.74. Formation of 8-membered ring by dehydrogenative coupling.

As showed in scheme 2.74, we attributed the success of the reaction to the probable formation of the intermediate **380**, in which the nitrogen atom on the tethering chain acted as an intramolecular chelating group for the palladium, bringing the aromatic counterpart in close proximity to the catalyst centre.

As the reaction was slightly varied from before, solvents were screened in order to find the best reaction condition for this specific transformation.

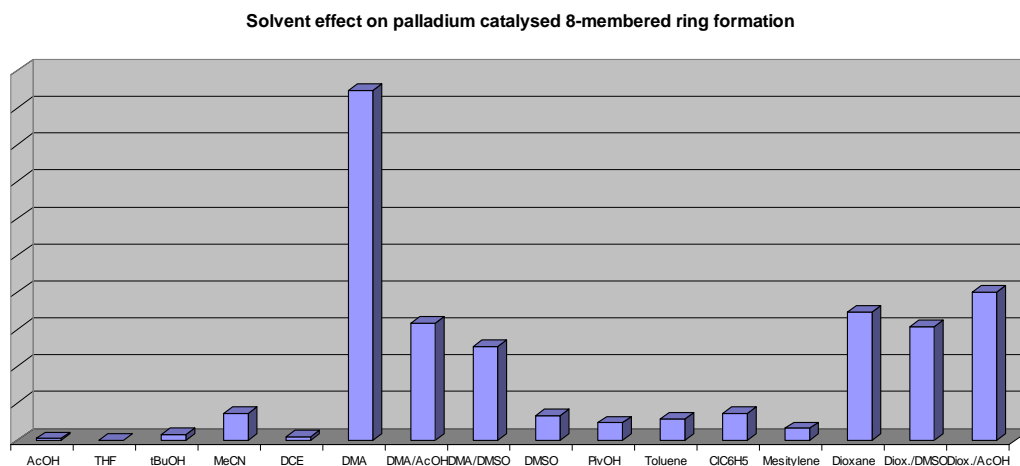
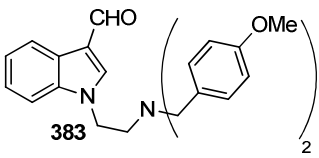
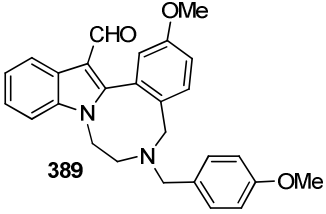
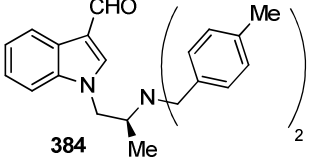
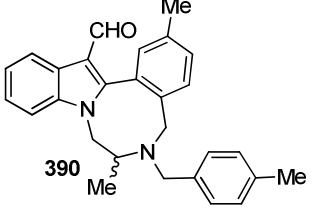
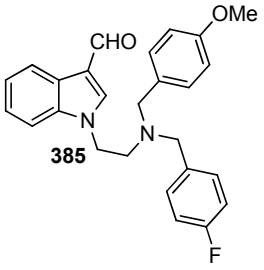
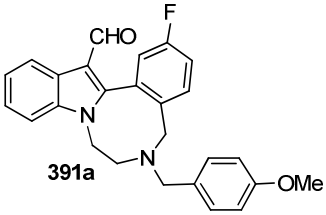
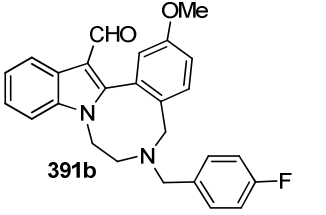
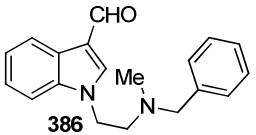
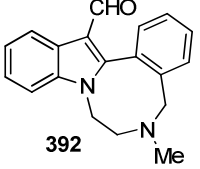
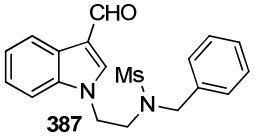
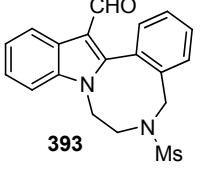
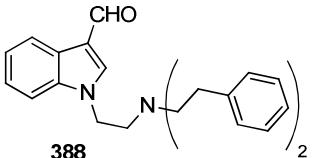
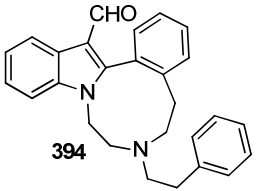


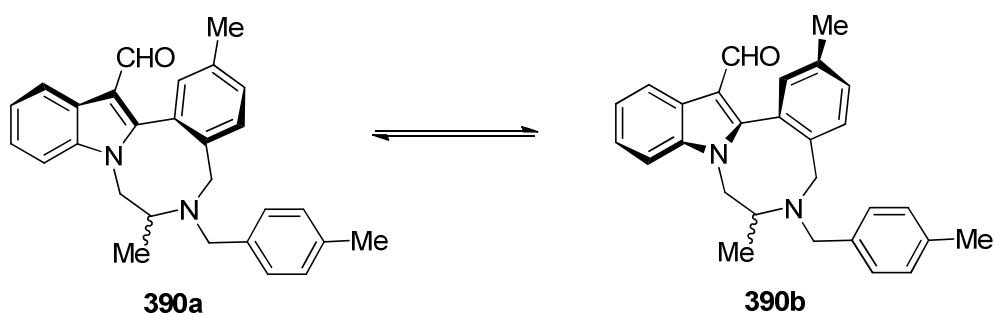
Figure 2.16. Solvent effect on palladium catalysed 8-membered ring reaction formation [ratio $\text{Pdr}_{\text{formed}}/\text{SM}_{\text{left after reaction}} = f(\text{solvents})$].

DMA was also found to be the best solvent for the reaction. Additives such as DMSO and AcOH, decreased the yield of product formed (Figure 2.16). The reaction seemed to occur under the same reaction conditions as mentioned before and was extended to a small range of examples (Table 2.12).

Table 2.12. Benzannulated 8-membered ring indoles.

| Entry | S.M. | Product | Yields (%) |
|-------|--|--|-----------------------|
| 1 |  383 |  389 | 55 |
| 2 |  384 |  390 | 51 |
| 3 |  385 |  391a | 62 |
| | |  391b | 391a : 391b = 1.6 : 1 |
| 3 |  386 |  392 | 37 |
| 4 |  387 |  393 | <10 |
| 5 |  388 |  394 | 0 |

Likewise substrate **379**, substrates containing substituted dibenzyl groups reacted well. Interestingly the reaction of **384** provided an inseparable pair of diastereomeric compounds **390**. Complete NMR characterisation of the product mixture showed that the bond connectivity was respected and that all the signals were induplicate. As the nitrogen inside of the eight membered ring could be considered as pseudo-chiral, we initially thought that a flipping of the nitrogen atom could result in the formation of two pseudo-diastereomeric products having two different NMR spectra. In order to check if the hypothesis of a nitrogen inversion theory was true, high temperature NMR study on the product mixture was performed. We hypothesised that a gain in temperature would make the molecule to flip faster and therefore the two NMR spectra previously obtained would merge to give one common signal. Surprisingly increasing the temperature did not result in the merging of the NMR signal but in a better separation of the two spectra. We reasoned that the pseudo-chirality of nitrogen atom was not directly involved in the generation of the products mixture. Eventually, we suggested that compound **390** could exist as a mixture of atropisomers and that an equilibrium between **390a** and **390b** exist, which could explain the complexity of the NMR spectrum (Scheme 2.75).¹²¹



Scheme 2.75. Mixtures of atropisomers **390**.

Starting material **385** proved to be a starting material of choice to get more insight into the mechanism of the reaction. In fact, compound **385** bore two different benzyl groups, one being electron-rich (*p*-OMe) and the other being electron-poor (*p*-F). This competition study gave a product distribution of 1.6 : 1 in favour of the cyclisation at the most electron-deficient arene **391a**.

As mentioned before, this indicated that acidic C-H bonds were more likely to react in the second palladation step and that a C-H activation mechanism was more to be considered rather than a S_EAr mechanism.

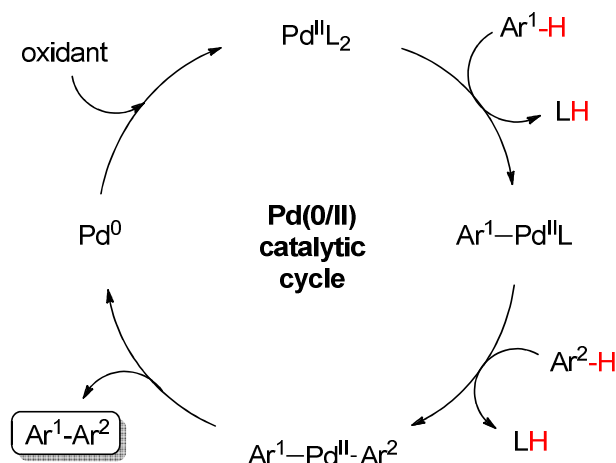
Compounds bearing a unique benzyl group and therefore containing only two sites for cyclisation proved to be less reactive than the dibenzylamine derivatives. This difference in reactivity could be rationalised by a simple statistical explanation, monobenzylated compounds having less cyclisation sites available for reaction than dibenzylated substrates.

Lastly, the formation of 9-membered ring system **394** was attempted but failed to produce any product. This could probably be explained by the fact that the tethered arene certainly pointed far away from the palladium centre after palladation of the indole.

8- and 9-membered ring systems were found to be far more difficult to synthesise than 7-membered rings by oxidative coupling reaction. Large transannular and torsional strain effects observed in substrates containing an aliphatic tethering chain made it impossible to prepare such rings. Substitution of the aliphatic tethering chain by a chain containing a chelating nitrogen atom allowed to prepare 8-membered ring compounds. Dibenzylamines proved to be good substrates for the reaction and a small series of diazocane derivatives could successfully be synthesised.

2.3.4 Mechanistic study

Palladium catalysed oxidative C-H / C-H coupling reaction often refers to palladium (0/II) catalytic systems. Catalyst generally introduced in the reaction as Pd(II)L₂ inserts selectively into the first C-H bond, displacing one of the ligand (Step 1). Then the second metalation with the other partner occurs, affording the intermediate Ar¹-Pd(II)-Ar², which can undergo reductive elimination, permitting the creation of a new carbon - carbon bond. Eventually, palladium (0) released in solution is re-oxidised to Pd(II) by an external oxidant to close the catalytic cycle (Scheme 2.76).



Scheme 2.76. Palladium (0/II) catalytic cycle in C-H activation.

Although the general drawing of the catalytic cycle in C-H / C-H coupling seems to be well-pictured by the organic, inorganic and computational chemists, a more precise understanding of each step of the process is not necessarily obvious.

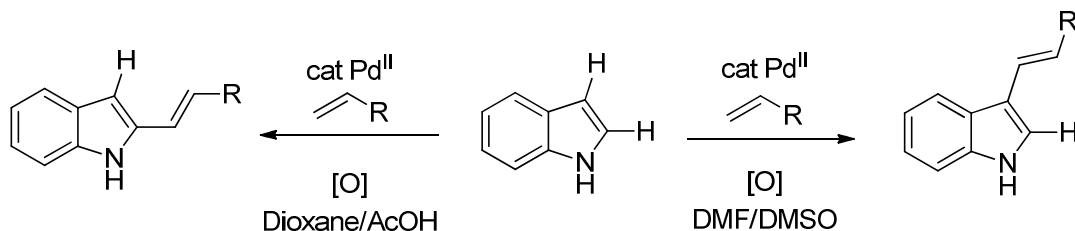
Indeed, the electronic and steric nature of palladium(II) between the first and second C-H activation can be considerably different, thereby the two C-H activation steps can proceed in different reaction mechanisms.

In our chemistry, we hypothesise that the first palladation step would occur at the most activated position which is the C(2) position of the indole and the C-H bond of the tethered aromatic part would be activated secondly. To prove the hypothesis and

obtain some mechanistic information of the two palladation steps, we conducted some trapping and deuterium experiments.

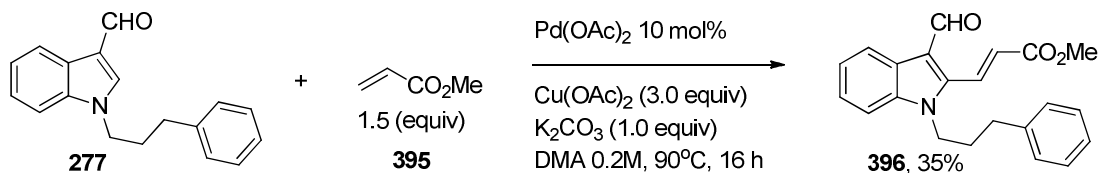
2.3.4.1 Trapping of the first palladation step

It is known that the reaction of heterocycles with alkenes in the presence of palladium (II) affords vinylheteroarenes though palladation of heteroarenes followed by Heck-type reaction. Indeed, Pd(II) catalysed Fujiwara-Moritani oxidative Heck reaction of activated alkenes with (benzo)furans and (benzo)thiophenes have been reported by Fujiwara in the 1980's¹²² and more recently in 2010 by Zhu.¹²³ Miura and co-workers also reported the oxidative alkenylation of azoles.¹²⁴ Eventually, indolizines and indoles were also used in the reaction by Zhang *et al.*¹²⁵ and Gaunt *et al.* work is highlighted in scheme 2.77.¹²⁶



Scheme 2.77. Solvent-controlled regioselective alkenylation reaction of indoles.

Using this chemistry, we expected that the first palladated intermediate could be trapped by an appropriate alkene to give the Heck-type product bearing the alkenyl group on the most reactive site. The reaction of the indole derivative **277** with methyl acrylate under our oxidative reaction conditions (DMA, Cu(OAc)₂, K₂CO₃) provided the vinyl product **396** in 35% yield (Scheme 2.78).



Scheme 2.78. Identification of the first palladation step by oxidative Heck trapping.

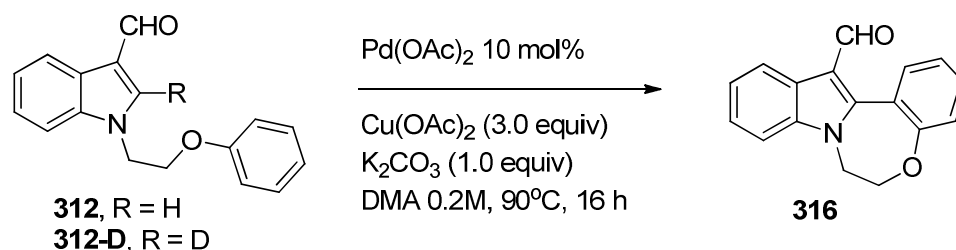
Although the yield of the product **396** was not very high, the reaction was very clean and did not provide any other alkenylated product. The regioselectivity of the

alkylation reaction suggested that the first C-H activation proceeded as expected at the most reactive indole position rather than at the end of the tethering chain.

2.3.4.2 Kinetic isotope studies

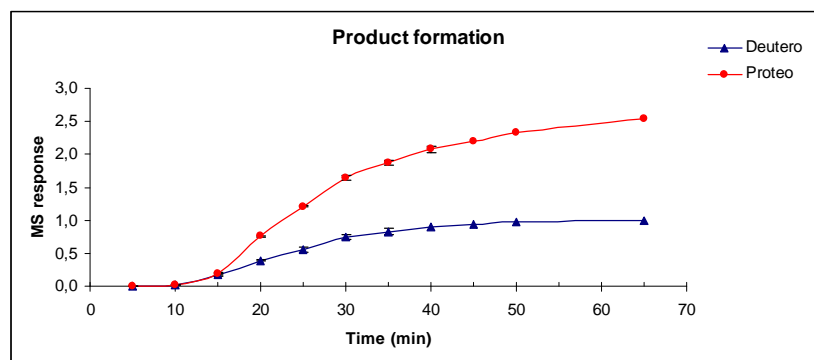
Knowing that the first step of the process was the palladation of the indole at the C(2) position we attempted to get some information regarding the mechanism of this specific step. Therefore, Kinetic Isotope Effect (KIE) studies have been carried out at the C(2) position in order to demonstrate if the breaking of this C-H bond was directly involved in the rate determining step of the reaction.^{96,127-132}

Being intramolecular, the reaction was considered to be first order in substrate, the indole derivative **312-D** deuterated at the C(2) position was prepared and the method of the initial rate of product formation **316** was used to determine the KIE. The formation of the product **316** was monitored over time by LCMS analysis (Scheme 2.79). Complete details regarding the samples preparation and the measurements can be found in the experimental section of this chapter.



Scheme 2.79. KIE experiment at the indole C(2) position.

A



B

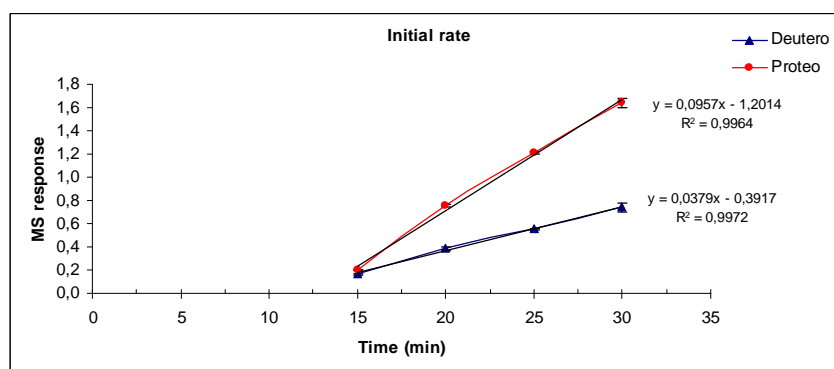


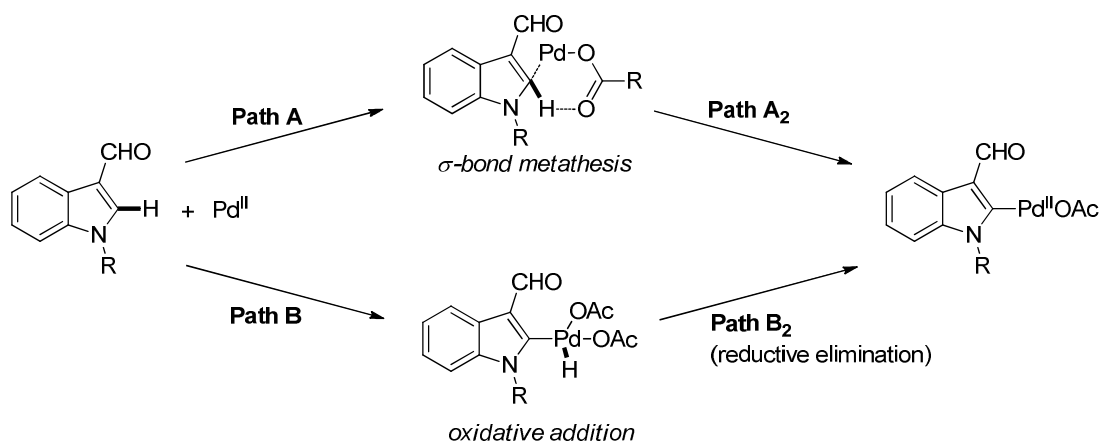
Figure 2.17. A) Product formation for proteo and deutero substrates versus time. B) Initial rate of product formation for proteo and deutero substrates

Initial rates for both substrates were determined by taking the linear part of the product formation curve (A) at the beginning of the reaction and the ratio between the two slopes gave the KIE.¹³²

Table 2.13. . Initial rates and KIE value at the C(2) position of the indole

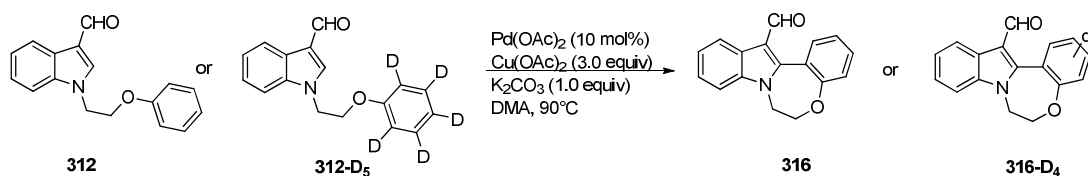
| Exp. | Proteo SM (312) | Deutero SM (312-D) | KIE |
|------|-----------------|--------------------|------|
| 1 | 0.0957 | 0.0379 | 2.52 |

KIE for 2-deutero indole derivative was 2.5 (k_H / k_D), a value large enough ($KIE > 2$) for the cleavage of the bond to be involved in the rate-limiting step. This also seemed to indicate that a σ -bond metathesis (path A) or an oxidative addition (path B) pathway would be likely to occur in this case as both required the participation of the C-deuterium/hydrogen bond in the transition state (Scheme 2.80).



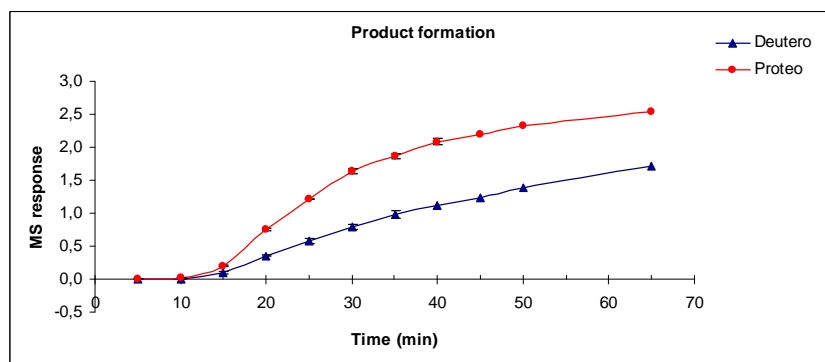
Scheme 2.80. Possible C-H activation reaction pathways.

Although experimental data showed that the palladation of the electron-deficient indole seemed to be the rate determining step of the reaction, we also performed a kinetic isotope study on the other part of the molecule in order to determine the mechanism involved in the second palladation step (Scheme 2.81).



Scheme 2.81. Intermolecular kinetic isotope effect (KIE) at the benzene position of the tethering chain.

A



B

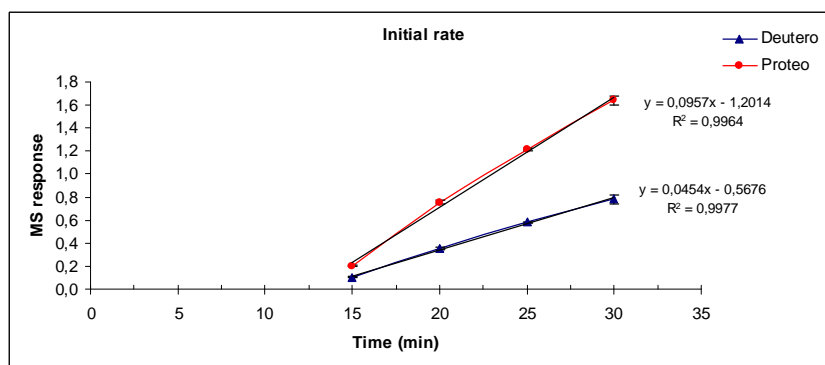


Figure 2.18. A) Product formation for proteo and deuterio (d₅) substrates versus time. B) Initial rate of product formation for proteo and deuterio (d₅) substrates

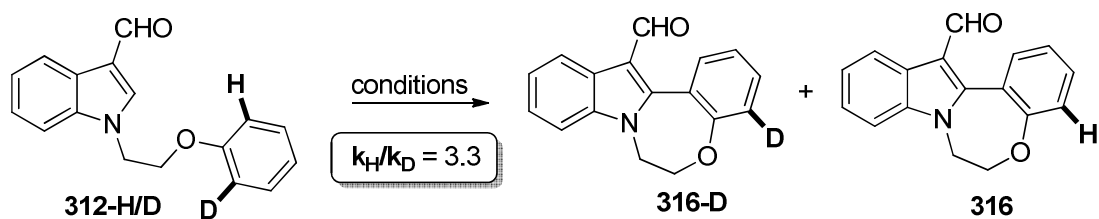
Table 2.14. Initial rates and KIE value.

| Exp. | Proteo SM (312) | Deutero SM (312-D ₅) | KIE |
|------|-----------------|----------------------------------|-------------|
| 1 | 0.0957 | 0.0454 | 2.10 |

Surprisingly, KIE obtained for the second step of the reaction was also equal to two. This indicated that the second palladation step was also involved in the rate determining step, which should not be possible considering the fact that the first step was already the rate limiting.

Considering these two sets of KIE experiments, it is not clear yet to conclude with real conviction about the mechanism of these two palladation steps.

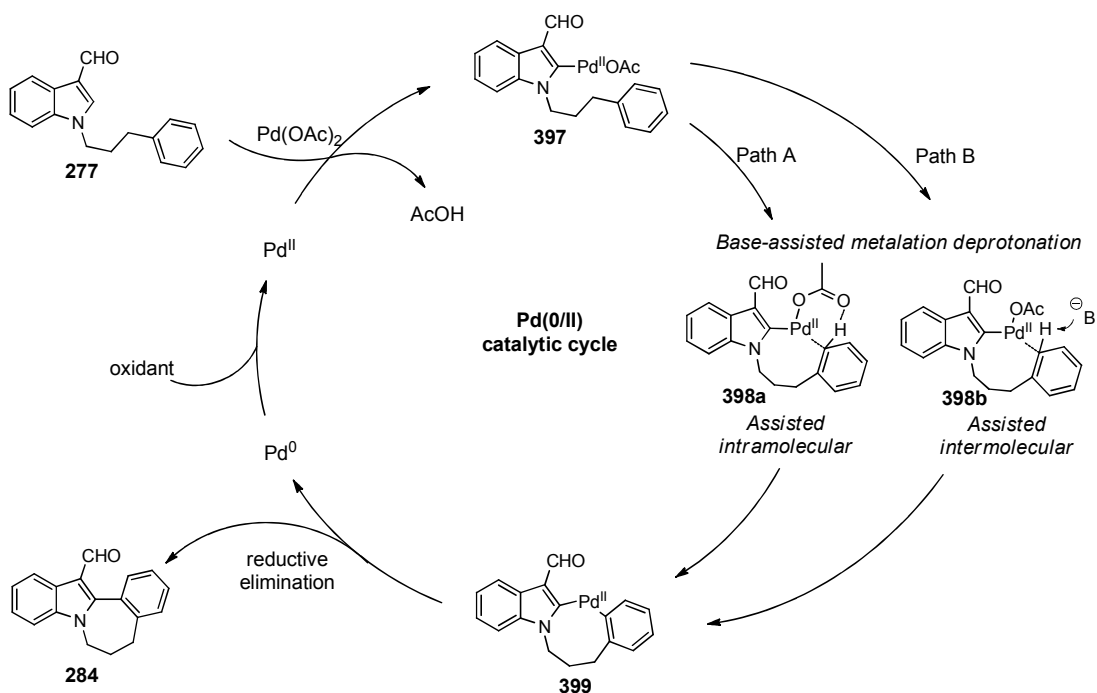
An intramolecular KIE experiment was also performed as highlighted in Scheme 2.82 but the results obtained did not provide any information regarding the rate determining step. Indeed, these experiments always have a competition between H/D regardless of the rate determining step, and thus should give an isotope effect no matter where it fall on the catalytic cycle.



Scheme 2.82. Intramolecular KIE study for the second palladation step.

2.3.4.3 Proposed mechanism

As mentioned earlier, it is difficult to get a detailed picture of each and every step of the mechanism of the reaction we developed. However, it is probably accurate to say that in the presence of palladium acetate, electron-deficient starting material gets palladated *via* either a C-H activation or a S_EAr mechanism giving the palladated indole **397**. Bearing in mind the selectivity obtained for the reaction of electron-poor substituted arenes such as *meta*-fluoro and *para*-fluoroarenes, an intramolecular C-H activation pathway rather than a S_EAr mechanism is more likely to happen in step two. But, it is not clear yet if a concerted-metalation-deprotonation (CMD) mechanism (path A) or if an intermolecular base-assisted deprotonation mechanism (path B) actually occurs to afford the 8-membered palladacycle **399**.¹³³⁻¹³⁶ This palladacycle can reductively eliminate to provide the final product **284** and palladium (0) is then re-oxidise to palladium (II) by excess copper (II) acetate (Scheme 2.83).



Scheme 2.83. Proposed catalytic cycle.

2.4 Conclusion and future work

We have successfully developed the first methodology for the synthesis of benzannulated medium ring heteroaromatics through C-H coupling. In contrast to the more facile 5-membered ring synthesis, medium rings synthesis has not been reported before using a metal catalysed oxidative cross-coupling approach. The process is rapid, efficient and do not require any pre-functionalisation of the substrate as two C-H bonds are selected to undergo efficient reaction to form a C-C bond under palladium catalysis. We exemplify the chemistry using heteroaromatic substrates such as indoles, benzimidazoles and pyrazoles at the core of numerous biologically active molecules. 7- and 8- membered ring systems bearing various functional groups have been chiefly targeted and obtained in good to excellent yields. The chemistry uses a catalytic system involving catalytic palladium (II) as the active species as well as copper (II) as external oxidant. Moreover, experimental data and mechanistic studies allow us to propose a Pd (II/0) catalytic cycle of the reaction. This first methodology in the field of oxidative coupling has recently been published in the Journal of American Chemical Society and could be the starting point for the development of other related work.

Indeed, we can imagine that the chemistry could be applied to the synthesis of other benzannulated indoles. For example, biologically active alkaloids such as Paullone **400**¹³⁷⁻¹⁴⁰ and Ibogamine **401** having a medium-sized ring fused between the C2 and C3 position of an indole scaffold could maybe be prepared by oxidative cross-coupling reaction (Figure 2.19).

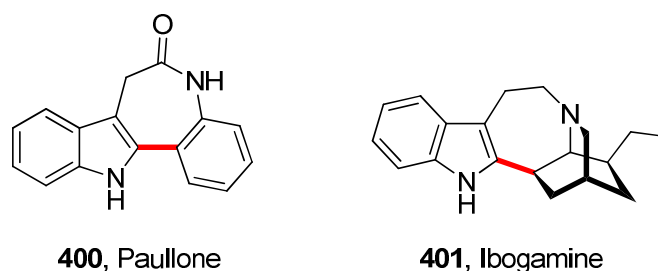
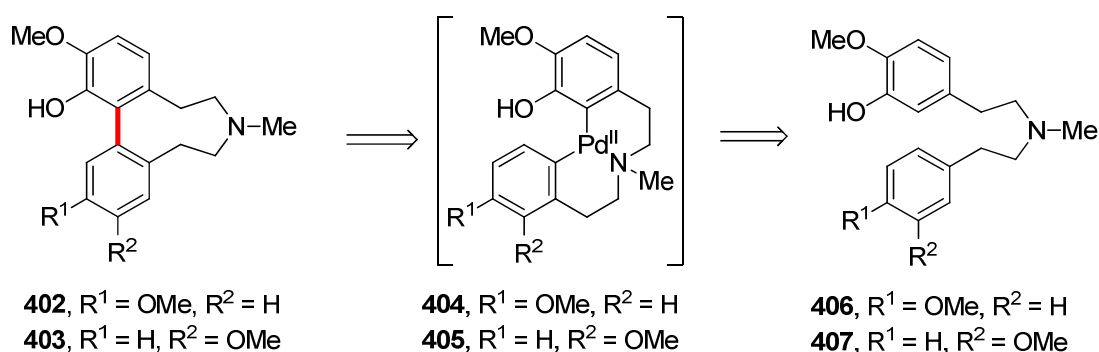


Figure 2. 19. Biologically active alkaloids containing medium-sized ring.

Moreover, the chemistry developed could maybe be extended to the formation of new arene-arene bonds within medium-sized ring systems. For instance, the alkaloids neodihydrothebaine **402** and bractazonine **403**, containing an azepane moiety could be synthesised using our chemistry (Scheme 2.84). Starting materials **406** and **407** would be easily prepared and we can imagine that the nitrogen joining the two tether chains would help during the palladation steps by stabilising the palladium species allowing the formation of a new C_{Ar}-C_{Ar} bond between the two arenes.



Scheme 2.84. Proposed retrosynthetic route for neodihydrothebaine **402** and bractazonine **403**.

It is noteworthy that if the chemistry prove to be successful, the synthesis of such benzofused azepane derivatives could be used as the key step in the synthesis of more complex and valuable molecules such as morphine, codeine and thebaine.¹⁴¹⁻¹⁴⁴

2.5 Experimental

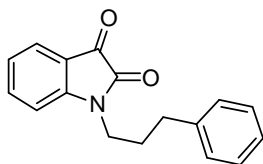
2.5.1 General

^1H and ^{13}C NMR spectra were recorded on a Bruker Ava500 (500 MHz) instrument and calibrated to residual solvent peaks: proton (CDCl_3 7.26 ppm) and carbon (CDCl_3 77.0 ppm). The ^1H data is presented as follows: chemical shift (in ppm on the δ scale), multiplicity (bs=broad singlet, s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet), the coupling constant (J, in Hertz) and integration. The ^{13}C data is reported as the ppm on the δ scale followed by the interpretation. Electrospray and electron impact high resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer. The data is recorded as the ionisation method followed by the calculated and measured masses. Melting points are uncorrected. TLC was performed on Merck 60F254 silica plates and visualised by UV light and/or anisaldehyde or potassium permanganate stains. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. The eluent is quoted as a percentage. The temperature of the reaction mixture was monitored using a calibrated infrared temperature control under the reaction vessel. Solvents for starting material preparation were dried before use unless otherwise stated. Anhydrous solvents used for the coupling reaction were bought from Sigma-Aldrich and used as received. All other chemicals were purchased from a chemical supplier and used as received.

2.5.2 By-products isolated

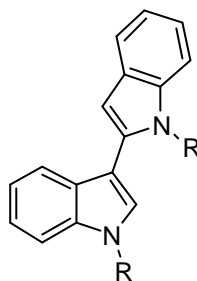
The two following compounds were obtained and isolated in several cases while screening the reaction conditions. Corresponding yields are not presented as they fluctuated depending on the reaction conditions used.

1-(3-Phenyl-propyl)-1*H*-indole-2,3-dione, (274). Orange oil. *R_f* [DCM/hexane



(1:1)] = 0.34. ¹H NMR (500 MHz, CDCl₃) δ 7.61 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.57 (td, *J* = 7.8, 1.3 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.25 – 7.19 (m, 3H), 7.16 – 7.10 (m, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 3.78 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.12 – 2.04 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 183.5 (quat), 158.2 (quat), 150.8 (quat), 140.5 (quat), 138.2 (CH), 128.5 (2CH), 128.3 (2CH), 126.3 (CH), 125.4 (CH), 123.67 (CH), 117.6 (quat), 110.0 (CH), 39.7 (CH₂), 33.0 (CH₂), 28.4 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₇H₁₆NO₂: 266.1176; found 266.1179.

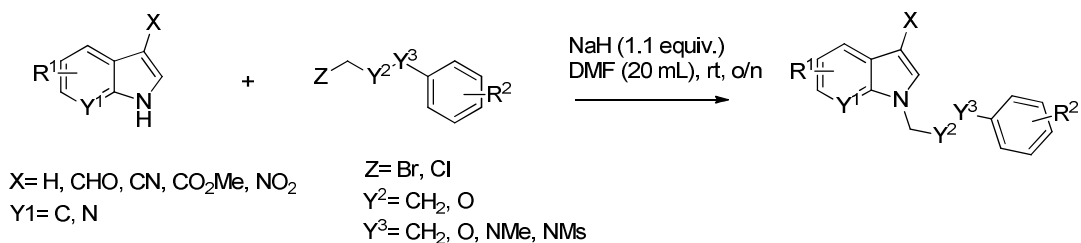
1,1'-Bis-(3-phenyl-propyl)-1*H*,1'*H*-[2,3']biindolyl, (275). Colourless oil. *R_f*



[DCM/hexane (4:6)] = 0.30. ¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.42 – 7.29 (m, 6H), 7.28 – 7.11 (m, 10H), 7.05 – 6.96 (m, 2H), 4.31 – 4.22 (m, 2H), 4.19 (t, *J* = 7.1 Hz, 2H), 2.78 – 2.67 (m, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.34 – 2.22 (m, 2H), 2.07 (dt, *J* = 15.2, 7.6 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 141.1 (quat), 140.7 (quat), 137.0 (quat), 136.1 (quat), 128.6 (quat), 128.6 (2CH), 128.4 (2CH), 128.3 (2CH), 128.2 (2CH), 128.0 (quat), 127.04 (CH), 126.29 (CH), 125.91 (CH), 122.28 (CH), 120.97 (CH), 120.38 (CH), 120.21 (CH), 119.5 (CH), 109.7 (CH), 109.6 (CH), 107.4 (quat), 102.1 (quat), 45.8 (CH₂), 43.5 (CH₂), 33.0 (CH₂), 32.9 (CH₂), 31.4 (CH₂), 31.3 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₃₄H₃₃N₂: 469.2638; found 469.2627.

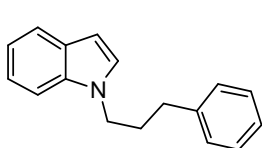
2.5.3 Preparation of starting materials

2.5.3.1 General procedure A:



Scheme 2.85. Preparation of *N*-alkyl indole starting materials.

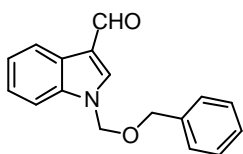
General procedure A for indole alkylation: Synthesis of 1-(3-Phenylpropyl)- 1H-



Indole, (272).¹⁴⁵ To a solution of NaH (376 mg, 9.40 mmol, 60 wt% in mineral oil) in dry DMF (50 mL) at 0 °C was added a solution of indole (1 g, 8.55 mmol) in dry DMF (5 mL), dropwise. The mixture was stirred at this temperature for 20 min. To the reaction mixture was added dropwise a solution of 1-bromo-3-phenylpropane (1.43 mL, 9.40mmol) in DMF (5 mL) and the resulting solution was stirred at room temperature for 16 hr. Saturated aqueous NaHCO₃ was added and the mixture then extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄. Filtration, concentration in vacuo and purification by silica gel chromatography (*n*-hexane/Et₂O = 7/3) gave the desired product in a 86% yield as a yellow oil with identical spectral data to that previously reported. *R_f* [Et₂O/hexane (1:1)] = 0.54. ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.28 – 7.18 (m, 4H), 7.17 – 7.11 (m, 2H), 6.54 (d, *J* = 2.9 Hz, 1H), 4.18 (t, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 7.1 Hz, 2H), 2.35 – 2.10 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 140.9 (quat), 135.9 (quat), 128.6 (quat), 128.5 (2CH), 128.4 (2CH), 127.8 (CH), 126.1 (CH), 121.4 (CH), 121.0 (CH), 119.3 (CH), 109.4 (CH), 101.1 (CH), 45.7 (CH₂), 33.0 (CH₂), 31.5 (CH₂).

Compounds **276**, **325**, **326**,¹⁴⁶ **277**, **370**,¹⁴⁷ **320**,¹⁴⁸ **368**,¹⁴⁹ **369**¹⁵⁰ and **372**¹⁵¹ were synthesised according to procedure A and spectral data obtained for these compounds matched the one previously reported in the literature.

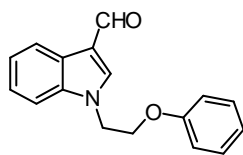
1-Benzylloxymethyl-1H-indole-3-carbaldehyde, (311). Prepared according to the



general procedure A using indole-3-carboxyaldehyde (1.0 g, 6.89 mmol), NaH (303 mg, 7.57 mmol, 60wt% in mineral oil) and benzyl chloromethyl ether (1.15 mL, 8.26 mmol). Column

system: hexane to hexane/Et₂O (2:3). Isolated as a white solid. Yield: 78%. Mp (Et₂O) = 79 °C. R_f [hexane / Et₂O (1:1)] = 0.12. ¹H NMR (500 MHz, CDCl₃) δ 10.06 (s, 1H), 8.50 – 8.22 (m, 1H), 7.77 (s, 1H), 7.56 (dd, *J* = 6.0, 2.6 Hz, 1H), 7.43 – 7.34 (m, 5H), 7.32 – 7.27 (m, 2H), 5.60 (s, 2H), 4.49 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 185.0 (quat), 138.3 (CH), 137.3 (quat), 136.2 (quat), 128.7 (2CH), 128.4 (2CH), 128.0 (CH), 125.6 (quat), 124.6 (CH), 123.5 (CH), 122.2 (CH), 119.1 (quat), 110.8 (CH), 75.8 (CH₂), 70.4 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₇H₁₆NO₂: 266.1176; found 266.1175.

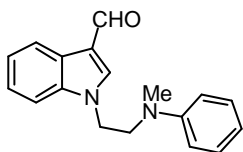
1-(2-Phenoxy-ethyl)-1H-indole-3-carbaldehyde, (312). Prepared according to the



general procedure A using indole-3-carboxyaldehyde (146.1 mg, 1.0 mmol), NaH (44 mg, 1.1 mmol, 60wt% in mineral oil) and (2-bromo-ethoxy)-benzene (200 mg, 1.0 mmol). Column

system: hexane to hexane/DCM (7:3). Isolated as a white solid. Yield: 76%. Mp (Et₂O) = 117 °C. R_f [hexane/DCM (7:3)] = 0.59. ¹H NMR (500 MHz, CDCl₃) δ 10.04 (s, 1H), 8.36 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.89 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.37 (dtd, *J* = 16.0, 7.2, 1.2 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 8.7, 0.9 Hz, 2H), 4.59 (t, *J* = 5.2 Hz, 2H), 4.35 (t, *J* = 5.2 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.7 (quat), 157.9 (quat), 139.2 (CH), 137.3 (quat), 129.7 (2CH), 125.4 (quat), 124.1 (CH), 123.1 (CH), 122.3 (CH), 121.7 (CH), 118.5 (quat), 114.5 (2CH), 109.8 (CH), 66.0 (CH₂), 46.5 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₇H₁₆NO₂: 266.1176; found 266.1172.

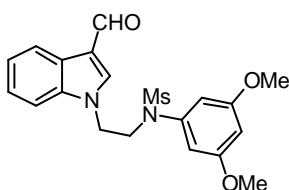
1-[2-(Methyl-phenyl-amino)-ethyl]-1H-indole-3-carbaldehyde, (313). Prepared



according to the general procedure A using indole-3-carboxyaldehyde (113 mg, 0.78 mmol), NaH (32 mg, 0.78 mmol, 60wt% in mineral oil) and (2-bromo-ethyl)-methyl-

phenyl-amine (167 mg, 0.78 mmol). Column system: hexane to DCM. Isolated as a white solid. Yield: 83%. Mp (Et₂O) = 107 °C. Rf [DCM] = 0.34. ¹H NMR (500 MHz, CDCl₃) δ 9.97 (s, 1H), 8.42 – 8.29 (m, 1H), 7.60 (s, 1H), 7.45 – 7.33 (m, 3H), 7.30 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 2H), 4.41 (t, *J* = 5.9 Hz, 2H), 3.81 (t, *J* = 5.9 Hz, 2H), 2.64 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 147.9 (quat), 139.0 (CH), 137.0 (quat), 129.6 (2CH), 125.5 (quat), 124.2 (CH), 123.1 (CH), 122.4 (CH), 118.6 (quat), 117.3 (CH), 112.1 (CH), 109.8 (CH), 52.3 (CH₂), 44.8 (CH₂), 39.0 (CH₃). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₈H₁₉N₂O: 279.1492; found 279.1491.

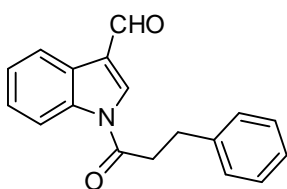
N-(3,5-Dimethoxy-phenyl)-N-[2-(3-formyl-indol-1-yl)-ethyl]-methanesulfonamide, (314).



Prepared according to the general procedure A using indole-3-carboxyaldehyde (213 mg, 1.47 mmol), NaH (65 mg, 1.61 mmol, 60wt% in mineral oil) and N-(2-Bromo-ethyl)-N-(3,5-dimethoxy-phenyl)-methanesulfonamide (505 mg, 1.50 mmol). Column

system: hexane to DCM/EtOAc (8:2). Isolated as a white solid. Yield: 60%. Mp (Et₂O) = 127 °C. Rf [DCM / EtOAc (9:1)] = 0.33. ¹H NMR (500 MHz, CDCl₃) δ 9.95 (s, 1H), 8.27 (dd, *J* = 6.5, 1.6 Hz, 1H), 7.69 (s, 1H), 7.43 – 7.21 (m, 3H), 6.37 (t, *J* = 2.2 Hz, 1H), 6.24 (d, *J* = 2.2 Hz, 2H), 4.42 (t, *J* = 6.5 Hz, 2H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.67 (s, 6H), 2.85 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 161.2 (quat), 140.9 (quat), 138.7 (CH), 137.1 (quat), 125.2 (quat), 124.3 (CH), 123.1 (CH), 122.2 (CH), 118.6 (quat), 110.0 (quat), 109.9 (CH), 106.1 (2CH), 100.3 (CH), 55.5 (2CH₃), 50.5 (CH₂), 46.6 (CH₂), 37.1 (CH₃). HRMS (ES⁺) calcd. for (M+H)⁺ C₂₀H₂₃O₅N₂S: 403.1322; found 403.1332.

1-(3-Phenyl-propionyl)-1H-indole-3-carbaldehyde, (319).

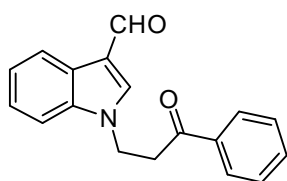


the general procedure A using indole-3-carboxyaldehyde (1.0 g, 6.89 mmol), NaH (303 mg, 7.57 mmol, 60wt% in mineral oil) and hydrocinnamoyl chloride (1.06 mL, 7.10 mmol). Column system: hexane to hexane/Et₂O (2:3).

Isolated as an orange oil. Yield: 83%. Rf [Et₂O/hexane (1:1)] = 0.24. ¹H NMR (500

MHz, CDCl₃) δ 10.09 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 8.38 – 8.25 (m, 1H), 8.06 (s, 1H), 7.51 – 7.41 (m, 2H), 7.38 – 7.28 (m, 5H), 3.37 – 3.31 (m, 2H), 3.23 (t, J = 7.5 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 185.5 (quat), 170.6 (quat), 139.7 (quat), 136.4 (quat), 134.5 (CH), 128.8 (2CH), 128.4 (2CH), 126.9 (CH), 126.7 (CH), 125.9 (quat), 125.4 (CH), 122.7 (quat), 121.9 (CH), 116.5 (CH), 37.8 (CH₂), 30.3 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₈H₁₆NO₂: 278.1176; found 278.1178.

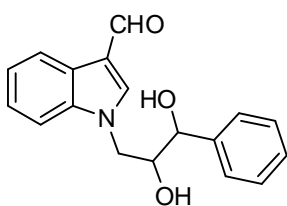
1-(3-Oxo-3-phenyl-propyl)-1H-indole-3-carbaldehyde, (321). Prepared according



to the general procedure A using indole-3-carboxyaldehyde (1.0 g, 6.89 mmol), NaH (303 mg, 7.57 mmol, 60wt% in mineral oil) and 3-chloro-1-phenyl-1-propanone (1.06 mL, 7.10 mmol). Column system: hexane to DCM. Isolated as a

colourless oil. Yield: 35%. R_f [DCM] = 0.23. ¹H NMR (500 MHz, CDCl₃) δ 9.98 (s, 1H), 8.33 (d, J = 7.6 Hz, 1H), 7.91 (dd, J = 5.6, 2.8 Hz, 3H), 7.58 (t, J = 7.4 Hz, 1H), 7.45 (dd, J = 12.8, 4.7 Hz, 3H), 7.40 – 7.29 (m, 2H), 4.67 (t, J = 6.4 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 196.8 (quat), 184.7 (quat), 139.7 (CH), 136.8 (quat), 136.0 (quat), 133.8 (CH), 128.8 (2CH), 128.0 (2CH), 125.4 (quat), 124.1 (CH), 123.0 (CH), 122.39 (CH), 118.2 (quat), 109.8 (CH), 41.6 (CH₂), 38.0 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₈H₁₆NO₂: 278.1162; found 278.1160.

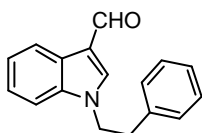
1-(2,3-Dihydroxy-3-phenyl-propyl)-1H-indole-3-carbaldehyde, (322). Prepared



according to the general procedure A and isolated as a colourless oil. Yield: 62%. R_f [EtOAc] = 0.62. ¹H NMR (500 MHz, MeOD) δ 9.82 (s, 1H), 8.17 (d, J = 6.5 Hz, 1H), 8.03 (s, 1H), 7.47 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz,

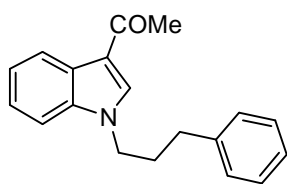
2H), 7.34 (t, J = 7.1 Hz, 1H), 7.31 – 7.19 (m, 3H), 4.66 (d, J = 3.6 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.23 – 3.98 (m, 2H). ¹³C NMR (126 MHz, MeOD) δ 185.5 (quat), 142.0 (CH), 141.5 (quat), 137.6 (quat), 128.0 (2CH), 127.4 (CH), 126.7 (2CH), 125.1 (quat), 123.5 (CH), 122.5 (CH), 121.3 (CH), 117.6 (quat), 110.2 (CH), 74.75 (CH), 73.7 (CH), 49.6 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₈H₁₈NO₃: 296.1281; found 296.1282.

1-Phenethyl-1H-indole-3-carbaldehyde, (323). Prepared according to the general



procedure A using indole-3-carboxyaldehyde (520 mg, 3.58 mmol), NaH (158 mg, 3.95 mmol, 60wt% in mineral oil) and (2-bromoethyl) benzene (533 uL, 3.94 mmol). Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 88%. Mp (Et₂O) = 65 °C. Rf [Et₂O/hexane (8:2)] = 0.40. ¹H NMR (500 MHz, CDCl₃) δ 9.91 (s, 1H), 8.35 (dd, *J* = 6.3, 2.3 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.24 (m, 3H), 7.08 – 7.02 (m, 2H), 4.43 (t, *J* = 7.1 Hz, 2H), 3.18 (t, *J* = 7.1 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.5 (quat), 138.7 (CH), 137.5 (quat), 136.9 (quat), 128.9 (2CH), 128.7 (2CH), 127.1 (CH), 125.5 (quat), 124.0 (CH), 123.0 (CH), 122.3 (CH), 118.0 (quat), 110.0 (CH), 49.0 (CH₂), 36.1 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₇H₁₆NO: 250.1226; found 250.1230.

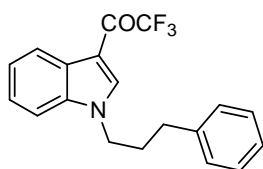
1-[1-(3-Phenyl-propyl)-1H-indol-3-yl]-ethanone, (327). Prepared according to the



general procedure A using 3-acetylindole (1.36 g, 8.55 mmol), NaH (376 mg, 9.40 mmol, 60wt% in mineral oil) and 1-bromo-3-phenylpropane (1.43 mL, 9.40mmol). Column system: hexane to hexane/Et₂O (2:8). Isolated as a colourless

oil. Yield: 47%. Rf [Et₂O/hexane (6:4)] = 0.22. ¹H NMR (500 MHz, CDCl₃) δ 8.45 – 8.40 (m, 1H), 7.72 (s, 1H), 7.38 – 7.31 (m, 5H), 7.29 – 7.25 (m, 1H), 7.20 (dd, *J* = 7.8, 0.9 Hz, 2H), 4.19 (t, *J* = 7.5 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.56 (s, 3H), 2.37 – 2.14 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 193.0 (quat), 140.2 (quat), 136.7 (quat), 134.8 (CH), 128.7 (2CH), 128.4 (2CH), 126.4 (CH), 123.3 (CH), 122.7 (CH), 122.6 (CH), 117.0 (quat), 109.8 (CH), 46.3 (CH₂), 32.8 (CH₂), 31.0 (CH₂), 27.7 (CH₃). HRMS (ES⁺) cald. for (M+H)⁺ C₁₈H₂₀NO: 278.1539; found 278.1543.

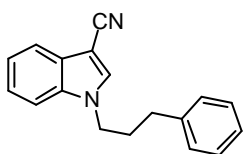
2,2,2-Trifluoro-1-[1-(3-phenyl-propyl)-1H-indol-3-yl]-ethanone, (328). Prepared



according to the general procedure A using 3-(trifluoroacetyl)indole (1.82 g, 8.55 mmol), NaH (376 mg, 9.40 mmol, 60wt% in mineral oil) and 1-bromo-3-phenylpropane (1.43 mL, 9.40mmol). Column system: hexane to hexane/Et₂O (2:3). Isolated as a white solid. Yield: 92%. Mp (Et₂O) = 103 °C. Rf

[Et₂O/hexane (1:1)] = 0.45. ¹H NMR (500 MHz, CDCl₃) δ 8.47 – 8.44 (m, 1H), 7.92 (q, *J* = 1.6 Hz, 1H), 7.45 – 7.33 (m, 5H), 7.31 – 7.26 (m, 1H), 7.21 (dd, *J* = 7.9, 0.9 Hz, 2H), 4.32 – 4.13 (m, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.40 – 2.24 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 174.74 (q, *J* = 34.8 Hz, quat), 139.80 (quat), 137.46 (q, *J* = 4.8 Hz, CH), 136.56 (quat), 128.77 (2CH), 128.38 (2CH), 127.18 (quat), 126.59 (CH), 124.57 (CH), 123.98 (CH), 122.79 (CH), 117.12 (q, *J* = 291.2 Hz, CF₃), 110.36 (CH), 109.48 (quat), 46.78 (CH₂), 32.60 (CH₂), 30.63 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₁₇NOF₃: 332.1257; found 332.1254.

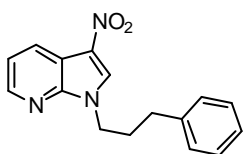
1-(3-Phenyl-propyl)-1H-indole-3-carbonitrile, (335). Prepared according to the



general procedure A using 3-cyanoindole (300 mg, 2.11 mmol), NaH (93 mg, 2.32 mmol, 60wt% in mineral oil) and bromo-3-phenylpropane (353 μL, 2.32 mmol). Column system: hexane to

hexane/Et₂O (2:3). Isolated as a white solid. Yield: 74%. Mp (Et₂O) = 50 °C. Rf [hexane / Et₂O (1:1)] = 0.30. ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.60 (s, 1H), 7.40 – 7.30 (m, 5H), 7.30 – 7.24 (m, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 4.19 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.34 – 2.19 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 140.0 (quat), 135.3 (quat), 134.6 (CH), 128.7 (2CH), 128.3 (2CH), 128.0 (quat), 126.5 (CH), 123.8 (CH), 122.2 (CH), 120.0 (CH), 116.0 (quat), 110.5 (CH), 85.7 (quat), 46.4 (CH₂), 32.7 (CH₂), 31.0 (CH₂). HRMS (ES⁺) cald. for (M+NH₄)⁺ C₁₈H₂₀N₃: 278.1652; found 278.1649.

3-Nitro-1-(3-phenyl-propyl)-1H-pyrrolo[2,3-b]pyridine, (336). Prepared

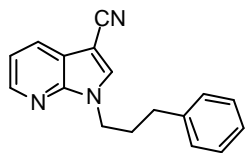


according to the general procedure A using 3-nitro-7-azaindole (250 mg, 1.53 mmol), NaH (67.4 mg, 1.68 mmol, 60wt% in mineral oil) and bromo-3-phenylpropane (255 μL, 1.68 mmol).

Column system: hexane to DCM. Isolated as a white solid. Yield: 56%. Mp (Et₂O) = 91 °C. Rf [DCM] = 0.42. ¹H NMR (500 MHz, CDCl₃) δ 8.57 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.49 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.20 (s, 1H), 7.39 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 7.19 (dd, *J* = 7.8, 0.9 Hz, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.43 – 2.26 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 145.8 (quat), 145.6 (CH), 140.1 (quat), 130.0 (CH), 129.4 (CH), 128.6 (2CH),

128.3 (2CH), 127.0 (quat) 126.4 (CH), 120.0 (CH), 113.9 (quat), 45.3 (CH₂), 32.8 (CH₂), 31.1 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₆H₁₆N₃O₂: 282.1237; found 282.1236.

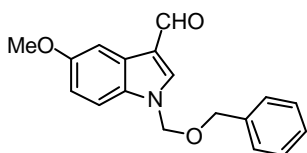
1-(3-Phenyl-propyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile, (342). Prepared



according to the general procedure A using 7-azaindole-3-carbonitrile (300 mg, 2.1 mmol), NaH (92 mg, 2.30 mmol, 60wt% in mineral oil) and bromo-3-phenylpropane (350 μL, 2.30 mmol). Column system: hexane to hexane/Et₂O (1:4). Isolated as a white solid.

Yield: 73%. Mp (Et₂O) = 65 °C. Rf [hexane / Et₂O (1:1)] = 0.23. ¹H NMR (500 MHz, CDCl₃) δ 8.48 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.73 (s, 1H), 7.35 – 7.25 (m, 3H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 4.39 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.9 Hz, 2H), 2.38 – 2.20 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 146.5 (quat), 145.2 (CH), 140.3 (quat), 135.0 (CH), 128.6 (2CH), 128.3 (2CH), 128.3 (CH), 126.3 (CH), 120.2 (quat), 118.2 (CH), 115.2 (quat), 84.3 (quat), 45.1 (CH₂), 32.8 (CH₂), 31.3 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₇H₁₆N₃: 262.1339; found 262.1335.

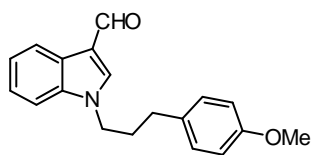
1-Benzyloxymethyl-5-methoxy-1H-indole-3-carbaldehyde, (348). Prepared



according to the general procedure A using methyl 7-methoxy-indole-3-carboxylate (875 mg, 5.0 mmol), NaH (220 mg, 5.5 mmol, 60wt% in mineral oil) and benzyl chloromethyl ether (1.3 mL, 9.16 mmol). Column system:

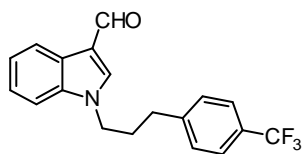
hexane to hexane/Et₂O (1:9). Isolated as a white solid. Yield: 92%. Mp (Et₂O) = 90 °C. Rf [hexane / Et₂O (2:8)] = 0.33. ¹H NMR (500 MHz, CDCl₃) δ 10.03 (s, 1H), 7.83 (d, *J* = 2.5 Hz, 1H), 7.72 (s, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.29 (dd, *J* = 5.4, 2.7 Hz, 2H), 7.02 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.57 (s, 2H), 4.48 (s, 2H), 3.93 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 185.0 (quat), 157.0 (quat), 138.4 (CH), 136.1 (quat), 132.0 (quat), 128.7 (2CH), 128.4 (CH), 128.0 (2CH), 126.4 (quat), 118.9 (quat), 115.0 (CH), 111.7 (CH), 103.4 (CH), 75.9 (CH₂), 70.3 (CH₂), 55.8 (CH₃). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₈H₁₈NO₃: 296.1281; found 296.1284.

1-[3-(4-Methoxy-phenyl)-propyl]-1H-indole-3-carbaldehyde, (350). Prepared



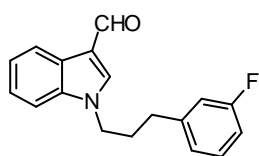
according to the general procedure A using indole-3-carboxyaldehyde (697 mg, 4.80 mmol), NaH (209 mg, 5.23 mmol, 60wt% in mineral oil) and 1-(3-bromopropyl)-4-methoxybenzene (1.0 g, 4.36 mmol). Column system: hexane to hexane/EtOAc (1:1). Isolated as a white solid. Yield: 66%. Mp (Et₂O) = 83 °C. Rf [EtOAc/hexane (35:65)] = 0.34. ¹H NMR (500 MHz, CDCl₃) δ 10.03 (s, 1H), 8.50 – 8.24 (m, 1H), 7.70 (s, 1H), 7.40 – 7.30 (m, 3H), 7.16 – 7.04 (m, 2H), 6.96 – 6.83 (m, 2H), 4.19 (t, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.33 – 2.18 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.5 (quat), 158.2 (quat), 138.2 (CH), 137.2 (quat), 132.1 (quat), 129.3 (2CH), 125.5 (quat), 124.0 (CH), 122.9 (CH), 122.2 (CH), 118.1 (quat), 114.1 (2CH), 110.1 (CH), 55.3 (CH₃), 46.4 (CH₂), 31.8 (CH₂), 31.1 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₂₀NO₂: 294.1489; found 294.1487.

1-[3-(4-Trifluoromethyl-phenyl)-propyl]-1H-indole-3-carbaldehyde, (351).



Prepared according to the general procedure A using indole-3-carboxyaldehyde (514 mg, 3.54 mmol), NaH (142 mg, 3.54 mmol, 60wt% in mineral oil) and 1-(3-bromopropyl)-4-trifluoromethyl-benzene (860 mg, 3.22 mmol). Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 88%. Mp (Et₂O) = 53 °C. Rf [Et₂O/hexane (7:3)] = 0.34. ¹H NMR (500 MHz, CDCl₃) δ 10.01 (s, 1H), 8.43 – 8.29 (m, 1H), 7.70 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.39 – 7.30 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.21 (t, *J* = 7.1 Hz, 2H), 2.79 – 2.67 (m, 2H), 2.35 – 2.20 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.5 (quat), 144.4 (d, *J* = 1.0 Hz, quat), 138.1 (CH), 137.1 (quat), 128.7 (2CH), 125.6 (q, *J* = 3.7 Hz, CH), 125.5 (quat), 124.2 (d, *J* = 271.9 Hz, quat), 124.1 (CH), 123.0 (CH), 122.2 (CH), 118.3 (quat), 110.0 (CH), 46.4 (CH₂), 32.6 (CH₂), 30.7 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₁₇NO₂F₃: 332.1257; found 332.1256.

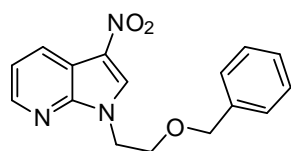
1-[3-(3-Fluoro-phenyl)-propyl]-1H-indole-3-carbaldehyde, (352). Prepared



according to the general procedure A using indole-3-carboxyaldehyde (280 mg, 1.93 mmol), NaH (78 mg, 1.93

mmol, 60wt% in mineral oil) and 1-(3-bromo-propyl)-3-fluoro-benzene (350 mg, 1.60 mmol). Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 72%. Mp (Et₂O) = 36 °C. Rf [Et₂O/hexane (7:3)] = 0.42. ¹H NMR (500 MHz, CDCl₃) δ 10.03 (s, 1H), 8.42 – 8.27 (m, 1H), 7.71 (s, 1H), 7.40 – 7.32 (m, 3H), 7.29 (td, *J* = 8.2, 6.1 Hz, 1H), 6.95 (td, *J* = 8.1, 2.6 Hz, 2H), 6.90 (dd, *J* = 9.8, 1.8 Hz, 1H), 4.22 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.38 – 2.19 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.5 (quat), 163.0 (d, *J* = 246.2 Hz, quat), 142.7 (d, *J* = 7.1 Hz, quat), 138.1 (CH), 137.1 (quat), 130.2 (d, *J* = 8.4 Hz, CH), 125.5 (quat), 124.1 (CH), 124.02 (d, *J* = 2.8 Hz, CH), 123.0 (CH), 122.2 (CH), 118.3 (quat), 115.19 (d, *J* = 21.1 Hz, CH), 113.4 (d, *J* = 21.0 Hz, CH), 110.0 (CH), 46.4 (CH₂), 32.5 (CH₂), 30.7 (CH₂).). HRMS (ES⁺) cald. for (M+H)⁺ C₁₈H₁₇NO₂F: 282.1289; found 282.1286.

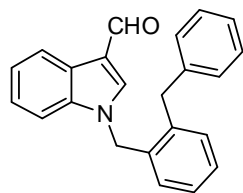
1-(2-Benzyloxy-ethyl)-3-nitro-1*H*-pyrrolo[2,3-*b*]pyridine, (371). Prepared



according to the general procedure A using 3-nitro-7-azaindole (250 mg, 1.53 mmol), NaH (67.4 mg, 1.68 mmol, 60wt% in mineral oil) and benzyl 2-bromoethyl ether (361 μL, 1.68 mmol). Column system: hexane to hexane/Et₂O

(1:9). Isolated as a white solid. Yield: 60%. Mp (Et₂O) = 95 °C. Rf [Et₂O/hexane (8:2)] = 0.42. ¹H NMR (500 MHz, CDCl₃) δ 8.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.44 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.39 (s, 1H), 7.37 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.25 – 7.19 (m, 2H), 4.65 – 4.56 (m, 2H), 4.52 (s, 2H), 3.92 – 3.81 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 145.7 (quat), 145.3 (CH), 137.2 (quat), 131.6 (CH), 129.3 (CH), 128.5 (2CH), 128.0 (CH), 127.7 (2CH), 127.0 (quat), 119.9 (CH), 113.8 (quat), 73.3 (CH₂), 67.8 (CH₂), 45.4 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₆H₁₆N₃O₃: 298.1183; found 298.1188.

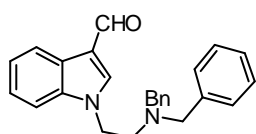
1-(2-Benzyl-benzyl)-1*H*-indole-3-carbaldehyde, (373). Prepared according to the



general procedure A using indole-3-carboxyaldehyde (280 mg, 1.93 mmol), NaH (78 mg, 1.93 mmol, 60wt% in mineral oil) and 2-benzyl-benzyl bromide (335 μL, 1.60 mmol). Column system: hexane to hexane/Et₂O (2:3). Isolated as a white solid. Yield:

51%. Mp (Et₂O) = 135 °C. Rf [Et₂O/hexane (1:1)] = 0.51. ¹H NMR (500 MHz, CDCl₃) δ 9.92 (s, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.21 (m, 9H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.25 (s, 2H), 4.06 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 139.5 (quat), 138.5 (quat), 138.4 (CH), 137.5 (quat), 133.4 (quat), 131.5 (CH), 128.8 (CH), 128.7 (2CH), 128.5 (2CH), 128.5 (CH), 127.53 (CH), 126.6 (CH), 125.4 (quat), 124.1 (CH), 123.1 (CH), 122.2 (CH), 118.4 (quat), 110.2 (CH), 48.4 (CH₂), 39.2 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₃H₂₀NO: 326.1539; found 326.1540.

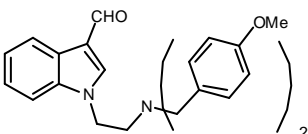
1-(2-Dibenzylamino-ethyl)-1*H*-indole-3-carbaldehyde, (379). Prepared according



to the general procedure A indole-3-carboxyaldehyde (156 mg, 1.07 mmol), NaH (47 mg, 1.18 mmol, 60wt% in mineral oil) and dibenzyl-(2-bromo-ethyl)-amine (295 mg, 0.97 mmol).

Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 77%. Mp (Et₂O) = 88 °C. Rf [Et₂O/hexane (7:3)] = 0.68. ¹H NMR (500 MHz, CDCl₃) δ 9.97 (s, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 7.54 (s, 1H), 7.37 – 7.14 (m, 12H), 7.01 (d, *J* = 8.2 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.68 (s, 4H), 2.93 (t, *J* = 6.4 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 139.1 (CH), 138.6 (quat), 137.2 (quat), 128.7 (4CH), 128.4 (4CH), 127.3 (2CH), 125.3 (quat), 123.8 (CH), 122.8 (CH), 122.1 (CH), 118.0 (quat), 109.8 (CH), 59.4 (2CH₂), 52.4 (CH₂), 45.6(CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₅H₂₅N₂O: 369.1961; found 369.1964.

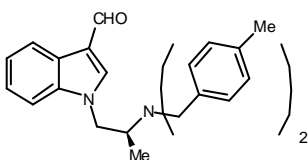
1-{2-[Bis-(4-methoxy-benzyl)-amino]-ethyl}-1*H*-indole-3-carbaldehyde, (383).



Prepared according to the general procedure A using indole-3-carboxyaldehyde (223 mg, 1.53 mmol), NaH (63 mg, 1.55 mmol, 60 wt% in mineral oil) and (2-Bromo-ethyl)-bis-(4-methoxy-benzyl)-amine (508 mg, 1.40 mmol). Column system: hexane to DCM/EtOAc (9:1). Isolated as a yellow oil. Yield: 68%. Rf [DCM] = 0.37. ¹H NMR (500 MHz, CDCl₃) δ 9.99 (s, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 7.56 (s, 1H), 7.35 – 7.24 (m, 1H), 7.24 – 7.14 (m, 1H), 7.09 (d, *J* = 8.6 Hz, 4H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 4H), 4.08 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 6H), 3.59 (s, 4H), 2.89 (t, *J* = 6.3 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ

184.5 (quat), 158.8 (2 quat), 139.3 (CH), 137.2 (quat), 130.6 (2 quat), 129.8 (4 CH), 125.3 (quat), 123.7 (CH), 122.7 (CH), 122.0 (CH), 117.9 (quat), 113.7 (4 CH), 109.9 (CH), 58.7 (2 CH₂), 55.3 (2 CH₃), 51.9 (CH₂), 45.7 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₇H₂₉N₂O₃: 429.2172; found 429.2172.

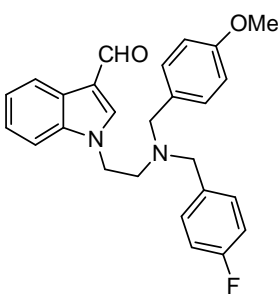
1-[(S)-2-[Bis-(4-methyl-benzyl)-amino]-propyl]-1H-indole-3-carbaldehyde,



(384). Prepared according to the general procedure A using indole-3-carboxyaldehyde (330 mg, 2.27 mmol), NaH (100 mg, 2.50 mmol, 60 wt% in mineral oil) and ((S)-2-Bromo-1-methyl-ethyl)-bis-(4-methyl-benzyl)-amine (692 mg,

2.00 mmol). Column system: hexane to hexane/Et₂O (2:3). Isolated as a yellow oil. Yield: 54%. R_f [Et₂O/Hexane (1:1)] = 0.36. ¹H NMR (500 MHz, CDCl₃) δ 9.98 (s, 1H), 8.34 (d, *J* = 7.9 Hz, 1H), 7.54 (s, 1H), 7.29 (dd, *J* = 9.1, 5.9 Hz, 1H), 7.18 – 7.08 (m, 1H), 7.00 (q, *J* = 8.1 Hz, 8H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.23 (dd, *J* = 14.3, 8.8 Hz, 1H), 3.97 (dd, *J* = 13.7, 6.7 Hz, 1H), 3.81 (d, *J* = 13.7 Hz, 2H), 3.51 – 3.28 (m, 3H), 2.31 (s, 6H), 1.14 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 139.9 (CH), 137.3 (quat), 136.6 (2 quat), 136.0 (2 quat), 127.0 (4 CH), 128.3 (4 CH), 125.3 (quat), 123.7 (CH), 122.6 (CH), 122.1 (CH), 117.7 (quat), 110.0 (CH), 53.1 (2 CH₂), 51.5 (CH), 50.6 (CH₂), 21.0 (2 CH₃), 10.6 (CH₃). HRMS (ES⁺) cald. for (M+H)⁺ C₂₈H₃₁N₂O: 411.2431; found 411.2430.

1-[2-[(4-Fluoro-benzyl)-(4-methoxy-benzyl)-amino]-ethyl]-1H-indole-3-

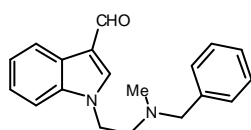


carbaldehyde, (385). Prepared according to the general procedure A using indole-3-carboxyaldehyde (130 mg, 0.89 mmol), NaH (36 mg, 0.89 mmol, 60 wt% in mineral oil) and (2-bromo-ethyl)-(4-fluoro-benzyl)-(4-methoxy-benzyl)-amine (283 mg, 0.81 mmol). Column system: hexane to hexane/EtOAc (2:8). Isolated as a yellow oil. Yield: 57%. R_f

[EtOAc/hexane (7:3)] = 0.49. ¹H NMR (500 MHz, CDCl₃) δ 9.99 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.56 (s, 1H), 7.29 (d, *J* = 6.7 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.15 – 7.06 (m, 4H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.89 (t, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 3.59 (s, 4H), 2.89 (t, *J* = 6.3 Hz, 2H). ¹³C

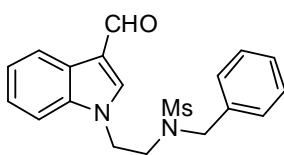
NMR (126 MHz, CDCl₃) δ 184.4 (quat), 161.9 (d, J = 245.4 Hz, quat), 158.9 (quat), 139.1 (CH), 137.1 (quat), 134.3 (quat), 134.3 (quat), 130.3 (quat), 130.0 (d, J = 7.9 Hz, 2CH), 129.8 (2CH), 125.3 (quat), 123.7 (CH), 122.8 (CH), 122.1 (CH), 118.0 (quat), 115.1 (d, J = 21.3 Hz, 2CH), 113.8 (2CH), 109.8 (CH), 58.5 (CH₂), 58.4 (CH₂), 55.2 (CH₃), 52.0 (CH₂), 45.6 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₆H₂₆N₂O₂F: 417.1973; found 417.1972.

1-[2-(Benzyl-methyl-amino)-ethyl]-1*H*-indole-3-carbaldehyde, (386). Prepared



according to the general procedure A using indole-3-carboxyaldehyde (200 mg, 1.38 mmol), NaH (61 mg, 1.51 mmol, 60 wt% in mineral oil) and Benzyl-(2-bromo-ethyl)-methyl-amine (409 mg, 1.79 mmol). Column system: hexane to hexane/EtOAc (2:3). Isolated as a yellow oil. Yield: 78%. R_f [EtOAc/Hexane (1:1)] = 0.23. ¹H NMR (500 MHz, CDCl₃) δ 10.02 (s, 1H), 8.34 (dd, J = 6.5, 1.9 Hz, 1H), 7.76 (s, 1H), 7.37 – 7.25 (m, 3H), 7.25 – 7.19 (m, 3H), 7.14 (dd, J = 6.8, 2.6 Hz, 2H), 4.25 (t, J = 6.3 Hz, 2H), 3.56 (s, 2H), 2.84 (t, J = 6.3 Hz, 2H), 2.37 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 139.2 (CH), 138.3 (quat), 137.3 (quat), 128.7 (2 CH), 128.3 (2CH), 127.2 (CH), 125.4 (quat), 123.8 (CH), 122.8 (CH), 122.1 (CH), 118.0 (quat), 109.8 (CH), 62.7 (CH₂), 55.6 (CH₂), 45.2 (CH₂), 42.6 (CH₃). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₂₁N₂O: 293.1648; found 293.1649.

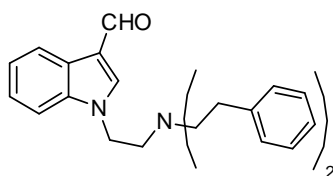
***N*-Benzyl-*N*-[2-(3-formyl-indol-1-yl)-ethyl]-methanesulfonamide, (387).** Prepared



according to the general procedure A using indole-3-carboxyaldehyde (200 mg, 1.38 mmol), NaH (61 mg, 1.51 mmol, 60 wt% in mineral oil) and benzyl-(2-bromo-ethyl)-mesyl-amine (468 mg, 1.79 mmol). Column system: hexane to DCM/EtOAc (2:3). Isolated as a yellow oil. Yield: 43%. R_f [DCM] = 0.17. ¹H NMR (500 MHz, CDCl₃) δ 9.95 (s, 1H), 8.27 (dd, J = 6.6, 2.0 Hz, 1H), 7.53 (s, 1H), 7.35 (dd, J = 5.0, 1.7 Hz, 3H), 7.32 – 7.27 (m, 2H), 7.24 (dd, J = 6.4, 3.1 Hz, 2H), 7.06 (dd, J = 6.8, 1.7 Hz, 1H), 4.22 (s, 2H), 4.22 – 4.17 (m, 2H), 3.56 – 3.46 (m, 2H), 2.86 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 138.5 (CH), 136.7 (quat), 135.2 (quat), 129.1 (2CH), 128.8 (2CH), 128.7 (CH), 125.3 (quat), 124.3 (CH), 123.1

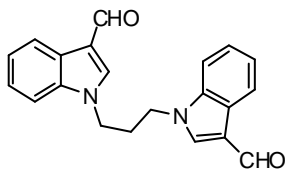
(CH), 122.3 (CH), 118.6 (quat), 109.7 (CH), 53.5 (CH₂), 47.3 (CH₂), 47.1 (CH₂), 37.5 (CH₃). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₂₁N₂O₃S: 357.1267; found 357.1268.

1-(2-Diphenethylamino-ethyl)-1H-indole-3-carbaldehyde, (388). Prepared



according to the general procedure A A indole-3-carboxyaldehyde (156 mg, 1.07 mmol), NaH (47 mg, 1.18 mmol, 60wt% in mineral oil) and di-ethyl-phenyl-(2-bromo-ethyl)-amine (320 mg, 0.97 mmol). Column system: hexane to DCM/EtOAc (2:3). Isolated as a white solid. Yield: 36%. Mp (Et₂O) = 79 °C. Rf [DCM] = 0.17. ¹H NMR (500 MHz, CDCl₃) δ 9.85 (s, 1H), 8.48 – 8.23 (m, 1H), 7.38 – 7.19 (m, 8H), 7.02 (d, *J* = 7.0 Hz, 4H), 6.91 (s, 1H), 4.04 (t, *J* = 5.7 Hz, 2H), 2.94 – 2.85 (m, 2H), 2.81 (t, *J* = 7.2 Hz, 4H), 2.59 (t, *J* = 7.2 Hz, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 184.9 (quat), 140.4 (CH), 140.3 (2quat), 136.9 (quat), 128.8 (4CH), 128.5 (4CH), 126.2 (2CH), 125.4 (quat), 123.8 (CH), 122.8 (CH), 122.4 (CH), 117.7 (quat), 109.6 (CH), 56.1 (2CH₂), 53.7 (CH₂), 45.8 (CH₂), 33.7 (2CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₇H₂₉N₂O: 397.2274; found 397.2273.

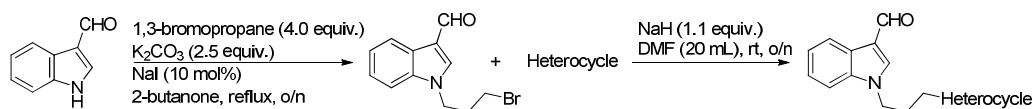
1,1'-(propane-1,3-diyl)bis(1H-indole-3-carbaldehyde), (359a). In a 100 mL round



bottom flask was introduced the indole-3-carboxyaldehyde (600 mg, 4.13 mmol, 2.2 equiv.), K₂CO₃ (656 mg, 4.74 mmol, 2.5 equiv.), 1,3-dibromopropane (222 uL, 1.9 mmol, 1.0 equiv.), a catalytic amount of NaI (29 mg, 10 mol%) and 40 mL of 2-butanone. The reaction mixture was refluxed for 16 hr and cooled down to room temperature. The inorganic salts were removed by filtration and the resulting filtrate was concentrated under vacuo. The crude mixture was purified by silica gel chromatography (ethyl acetate) and the final product was isolated in 81% yield as a white solid. Mp (Et₂O) = 157 °C. Rf [EtOAc/DCM (3:7)] = 0.30. ¹H NMR (500 MHz, CDCl₃) δ 10.01 (s, 2H), 8.36 (dd, *J* = 6.2, 2.8 Hz, 2H), 7.65 (s, 2H), 7.41 – 7.32 (m, 4H), 7.24 (dd, *J* = 6.2, 2.5 Hz, 2H), 4.25 (t, *J* = 6.9 Hz, 4H), 2.60 (p, *J* = 6.9 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.5 (2 quat), 137.5 (2 CH), 136.9 (2 quat), 125.5 (2 quat), 124.4 (2 CH), 123.3 (2 CH), 122.5 (2 CH), 118.7 (2 quat),

109.7 (2 CH), 44.0 (2CH₂), 29.5 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₂₁H₁₉N₂O₂: 331.1441; found 331.1438.

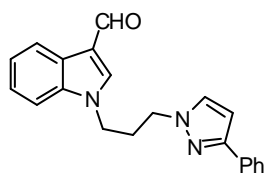
2.5.3.2 General procedure B:



Scheme 2.86. Synthesis of N-alkyl indole substrates containing heteroaromatic groups.

1-(3-Bromo-propyl)-1H-indole-3-carbaldehyde, (357). In a 500 mL round bottom flask was introduced the indole-3-carboxyaldehyde (5.0 g, 34.4 mmol, 1.0 equiv.), K₂CO₃ (12 g, 86.0 mmol, 2.5 equiv.), 1,3-dibromopropane (14 mL, 138 mmol, 4.0 equiv.), catalytic amount of NaI (516 mg, 10 mol%) and 250 mL of 2-butanone. The reaction mixture was refluxed for 16 hrs and cooled down to room temperature. The inorganic salts were removed by filtration and the resulting filtrate was concentrated under vacuo. The crude mixture was purified by silica gel chromatography (DCM) and the final product was obtained in 85% yield as yellow liquid. R_f [DCM] = 0.30. ¹H NMR (500 MHz, CDCl₃) δ 10.00 (s, 1H), 8.33 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.77 (d, *J* = 3.2 Hz, 1H), 7.43 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 4.40 (t, *J* = 6.6 Hz, 2H), 3.41 – 3.26 (m, 2H), 2.51 – 2.30 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 138.6 (CH), 137.0 (quat), 125.5 (quat), 124.2 (CH), 123.1 (CH), 122.3 (CH), 118.3 (quat), 110.0 (CH), 44.9 (CH₂), 32.0 (CH₂), 29.9 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₂H₁₃NOBr: 266.0175; found 266.0170.

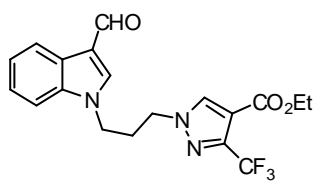
General procedure B: 1-[3-(3-Phenyl-pyrazol-1-yl)-propyl]-1H-indole-3-carbaldehyde, (359b).



To a solution of NaH (93 mg, 2.32 mmol, 60 wt% in mineral oil) in dry DMF (20 mL) at 0 °C was added dropwise a solution of 3-phenyl-1H-pyrazole (304 mg, 2.11 mmol) in dry DMF (2 mL). The mixture was stirred at this temperature for 20 min. To the reaction mixture was added dropwise a

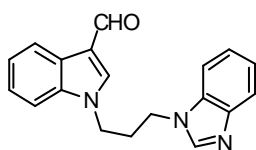
solution of 1-(3-bromo-propyl)-1H-indole-3-carbaldehyde (673 mg, 2.53 mmol) in DMF (2 mL) and the resulting solution was stirred at room temperature for 16 hr. Saturated aqueous NaHCO₃ was added and the mixture then extracted with ethyl acetate. The organic layer was washed with brine and dried over MgSO₄. Filtration, concentration in vacuo and purification by silica gel chromatography (EtOAc/MeOH = 9/1) gave the desired product in 51% yield as a white solid. Mp (Et₂O) = 96 °C. Rf [Et₂O/hexane (8:2)] = 0.22. ¹H NMR (500 MHz, CDCl₃) δ 10.02 (s, 1H), 8.36 (d, *J* = 4.6 Hz, 1H), 8.06 – 7.72 (m, 3H), 7.57 – 7.30 (m, 7H), 6.63 (s, 1H), 4.28 (t, *J* = 6.5 Hz, 2H), 4.16 (t, *J* = 5.9 Hz, 2H), 2.64 – 2.38 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 151.9 (quat), 139.0 (CH), 137.1 (quat), 133.4 (quat), 130.9 (CH), 128.8 (2CH), 127.9 (CH), 125.6 (2CH), 125.5 (quat), 124.1 (CH), 123.1 (CH), 122.3 (CH), 118.3 (quat), 110.1 (CH), 103.1 (CH), 48.6 (CH₂), 44.1 (CH₂), 30.2(CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₁H₂₀N₃O: 330.1601; found 330.1600.

1-[3-(3-Formyl-indol-1-yl)-propyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester, (359c).



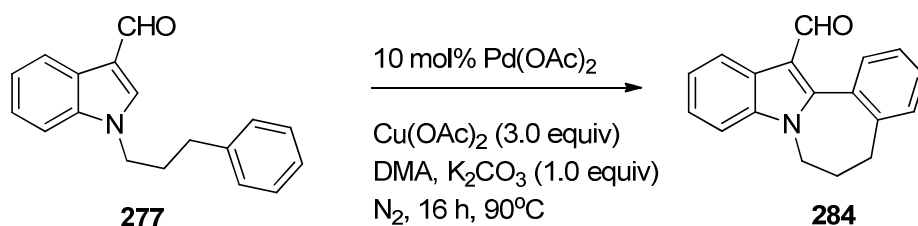
acid ethyl ester, (359c). Prepared according to the general procedure B using ethyl 3- (trifluoromethyl)-1H-pyrazole-4-carboxylate (439 mg, 2.11 mmol), NaH (93 mg, 2.32 mmol, 60 wt% in mineral oil) and 1-(3-bromo-propyl)-1H-indole-3-carbaldehyde (673 mg, 2.53 mmol). Column system: hexane to hexane/Et₂O (9:1). Isolated as a white solid. Yield: 48%. Mp (Et₂O) = 75 °C. Rf [Et₂O/hexane (8:2)] = 0.23. ¹H NMR (500 MHz, CDCl₃) δ 9.94 (s, 1H), 8.28 (d, *J* = 7.1 Hz, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.47 – 7.20 (m, 3H), 4.41 – 4.21 (m, 4H), 4.16 (t, *J* = 6.5 Hz, 2H), 2.63 – 2.39 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 160.6 (quat), 141.9 (q, *J* = 38.5 Hz, quat), 138.6 (CH), 136.9 (quat), 135.9 (CH), 125.4 (quat), 124.3 (CH), 123.1 (CH), 122.2 (CH), 121.5 (quat), 118.4 (quat), 113.4 (quat), 109.9 (CH), 61.0 (CH₂), 49.6 (CH₂), 43.9 (CH₂), 29.7 (CH₂), 14.0 (CH₃). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₁₉N₃O₃F₃: 394.1373; found 394.1371.

1-[3-(1H-Benzoimidazol-2-yl)-propyl]-1H-indole-3-carbaldehyde, (359d).



Prepared according to the general procedure B using benzimidazole (250 mg, 2.11 mmol), NaH (93 mg, 2.32 mmol, 60 wt% in mineral oil) and 1-(3-bromo-propyl)-1H-indole-3-carbaldehyde (673 mg, 2.53 mmol). Column system: hexane to EtOAc/MeOH (8:2). Isolated as a white solid. Yield: 86%. Mp (Et₂O) = 107 °C. R_f [EtOAc/MeOH (85:15)] = 0.22. ¹H NMR (500 MHz, CDCl₃) δ 10.02 (s, 1H), 8.42 – 8.27 (m, 1H), 8.01 (s, 1H), 7.87 (dd, *J* = 6.4, 2.5 Hz, 1H), 7.67 (s, 1H), 7.40 – 7.23 (m, 6H), 4.25 (m, 4H), 2.60 (p, *J* = 6.9 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.5 (quat), 143.6 (quat), 142.6 (CH), 137.7 (CH), 136.9 (quat), 133.3 (quat), 125.5 (quat), 124.4 (CH), 123.5 (CH), 123.3 (CH), 122.8 (CH), 122.5 (CH), 120.6 (CH), 118.7 (quat), 109.7 (CH), 109.4 (CH), 44.1 (CH₂), 42.0 (CH₂), 29.4 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₉H₁₈N₃O: 304.1444; found 304.1442.

2.5.4 C-H/C-H coupling reaction

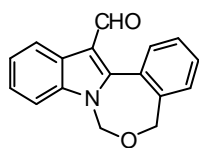


Scheme 2.87. Representative procedure for dehydrogenative coupling.

General procedure C for dehydrogenative coupling: Synthesis of 6,7-Dihydro-5H-benzo[3,4]azepino[1,2-a]indole-13-carbaldehyde, (**284**).

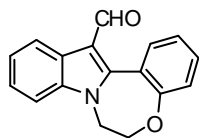
A screw cap test tube (100*11 mm) was loaded with finely crushed compound **277** (53 mg, 0.2 mmol), K₂CO₃ (28.0 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol) and Cu(OAc)₂ (109.0 mg, 0.6 mmol). Anhydrous DMA (1 mL) was then added and the tube was flushed with nitrogen before being sealed. The reaction mixture was allowed to stir at room temperature until the starting material completely dissolved before being placed into a pre-thermostated carrousel at 90 °C for 16 hr. The mixture was allowed to cool down and directly poured on top of a long silica gel chromatography column. The product was eluted with a mixture hexane/Et₂O (50:50). Pure product was obtained in 77% yield as a white solid. Mp (Et₂O) = 126 °C. R_f [hexane / Et₂O (4:6)] = 0.40. ¹H NMR (500 MHz, CDCl₃) δ 10.07 (s, 1H), 8.52 (d, *J* = 6.9 Hz, 1H), 7.63 (d, *J* = 6.4 Hz, 1H), 7.56 – 7.31 (m, 6H), 4.46 (bs, 1H), 3.81 (bs, 1H), 2.79 - 2.70 (m, 2H), 2.52 (bs, 1H), 2.36 – 2.15 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 186.2 (quat), 150.7 (quat), 139.4 (quat), 136.1 (quat), 131.5 (CH), 130.4 (CH), 129.7 (CH), 129.5 (quat), 127.1 (CH), 125.6 (quat), 123.9 (CH), 123.0 (CH), 122.6 (CH), 114.1 (quat), 109.0 (CH), 41.0 (CH₂), 31.3 (CH₂), 30.6 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₈H₁₅NO: 262.1226; found 262.1233.

5H-6-Oxa-7a-aza-dibenzo[a,e]azulene-12-carbaldehyde, (315). Prepared



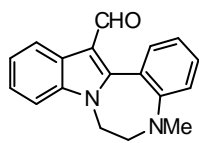
according to the general procedure C using compound **311** (53 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/ Et_2O (2:8). Isolated as a white solid. Yield: 70%. Mp (Et_2O) = 238 °C. Rf [hexane / Et_2O (1:1)] = 0.33. 1H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.51 (dd, J = 6.9, 1.5 Hz, 1H), 7.85 – 7.77 (m, 1H), 7.68 – 7.61 (m, 2H), 7.61 – 7.56 (m, 1H), 7.57 – 7.51 (m, 1H), 7.49 – 7.37 (m, 2H), 5.52 (s, 2H), 4.65 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.2 (quat), 149.4 (quat), 135.6 (quat), 134.3 (quat), 131.1 (CH), 130.9 (CH), 130.9 (CH), 130.4 (quat), 129.7 (CH), 125.8 (quat), 124.7 (CH), 123.7 (CH), 122.7 (CH), 114.5 (quat), 109.3 (CH), 69.6 (CH_2), 68.2 (CH_2). HRMS (ES^+) cald. for $(M+H)^+$ $C_{17}H_{14}NO_2$: 264.1019; found 264.1021.

6,7-Dihydro-5-oxa-7a-aza-dibenzo[a,e]azulene-12-carbaldehyde, (316). Prepared



according to the general procedure C using compound **312** (53 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to DCM. Isolated as a white solid. Yield: 63%. Mp (Et_2O) = 188 °C. Rf [DCM] = 0.29. 1H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.65 – 8.42 (m, 1H), 7.66 (dd, J = 7.6, 1.5 Hz, 1H), 7.55 (td, J = 7.8, 1.6 Hz, 1H), 7.46 – 7.33 (m, 4H), 7.33 – 7.26 (m, 1H), 4.67 (t, J = 5.7 Hz, 2H), 4.38 (t, J = 5.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.9 (quat), 154.1 (quat), 148.0 (quat), 135.7 (quat), 132.5 (CH), 132.1 (CH), 125.9 (quat), 124.9 (CH), 124.2 (CH), 123.4 (quat), 123.2 (CH), 123.2 (CH), 122.7 (CH), 108.6 (CH), 74.7 (CH_2), 41.5 (CH_2). HRMS (ES^+) cald. for $(M+H)^+$ $C_{17}H_{14}NO_2$: 264.1019; found 264.1022.

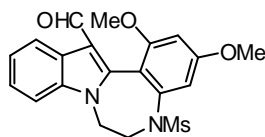
5-Methyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a]indole-13-



carbaldehyde, (317). Prepared according to the general procedure C using compound **313** (56 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6

mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 78%. Mp (Et₂O) = 186 °C. R_f [Et₂O/hexane (65:35)] = 0.24. ¹H NMR (500 MHz, CDCl₃) δ 10.01 (s, 1H), 8.52 (dd, *J* = 6.4, 2.3 Hz, 1H), 7.62 – 7.46 (m, 2H), 7.46 – 7.31 (m, 3H), 7.25 – 7.11 (m, 2H), 4.32 (bs, 2H), 3.62 (bs, 2H), 2.86 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 186.3 (quat), 150.3 (quat), 148.0 (quat), 135.5 (quat), 132.7 (CH), 131.5 (CH), 125.8 (quat), 123.7 (CH), 123.2 (quat), 123.0 (CH), 122.6 (CH), 122.1 (CH), 119.7 (CH), 114.0 (quat), 108.4 (CH), 60.4 (CH₂), 41.1 (CH₃), 41.1 (CH₂). HRMS (ES⁺) calcd. for (2M+H)⁺ C₃₆H₃₃N₄O₂: 553.2598; found 553.2593.

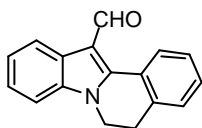
5-Methanesulfonyl-1,3-dimethoxy-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[7,1-a] indole-13-carbaldehyde, (318). Prepared according to the



general procedure C using compound **314** (81 mg, 0.2 mmol), K₂CO₃ (28.0 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol),

Cu(OAc)₂ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to DCM/EtOAc (9:1). Isolated as a white solid. Yield: 87%. Mp (Et₂O) = 190 °C. R_f [DCM / EtOAc (9:1)] = 0.61. ¹H NMR (500 MHz, CDCl₃) δ 10.00 (s, 1H), 8.44 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.45 – 7.32 (m, 3H), 6.89 (d, *J* = 2.3 Hz, 1H), 6.72 (d, *J* = 2.3 Hz, 1H), 4.50 (ddd, *J* = 28.4, 12.2, 8.6 Hz, 2H), 4.05 – 3.90 (m, 5H), 3.86 (s, 3H), 2.15 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 186.5 (quat), 163.0 (quat), 158.5 (quat), 142.3 (quat), 137.3 (quat), 135.6 (quat), 125.4 (quat), 124.1 (CH), 123.4 (CH), 122.7 (CH), 115.0 (quat), 110.6 (quat), 110.0 (CH), 108.6 (CH), 100.5 (CH), 56.1 (CH₃), 55.9 (CH₃), 53.1 (CH₂), 40.1 (CH₂), 38.6 (CH₃). HRMS (ES⁺) calcd. for (M+H)⁺ C₂₀H₂₁O₅N₂S₁: 401.1166; found 401.1166.

5,6-Dihydro-indolo[2,1-a]isoquinoline-12-carbaldehyde, (324). Prepared

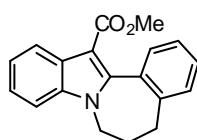


according to the general procedure C using compound **323** (50 mg, 0.2 mmol), K₂CO₃ (28.0 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Cu(OAc)₂ (109.0 mg, 0.6 mmol) and anhydrous DMA (1

mL). Column system: hexane to hexane/Et₂O (2:3). Isolated as a white solid. Yield: 87%. Mp (Et₂O) = 122 °C. R_f [Et₂O/hexane (1:1)] = 0.34. ¹H NMR (500 MHz, CDCl₃) δ 10.54 (s, 1H), 8.56 – 8.42 (m, 1H), 7.98 (dd, *J* = 5.4, 3.6 Hz, 1H), 7.48 –

7.43 (m, 2H), 7.43 – 7.39 (m, 2H), 7.35 (dtd, $J = 14.0, 6.9, 1.5$ Hz, 2H), 4.27 (t, $J = 6.5$ Hz, 2H), 3.20 (t, $J = 6.5$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 185.6 (quat), 143.1 (quat), 135.8 (quat), 135.0 (quat), 130.0 (CH), 129.0 (CH), 128.5 (CH), 127.8 (CH), 127.1 (quat), 126.7 (quat), 124.0 (CH), 123.3 (CH), 122.4 (CH), 113.4 (quat), 109.2 (CH), 40.1 (CH_2), 29.2 (CH_2).). HRMS (ES^+) calcd. for $(\text{M}+\text{H})^+ \text{C}_{17}\text{H}_{14}\text{NO}$: 248.1069; found 248.1067.

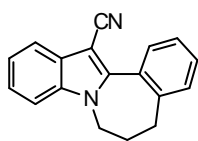
6,7-Dihydro-5H-benzo[3,4]azepino[1,2-a]indole-13-carboxylic acid methyl ester



(329). Prepared according to the general procedure C using compound **325** (59 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol), $\text{Cu}(\text{OAc})_2$ (109.0 mg, 0.6 mmol)

and anhydrous DMA (1 mL). Column system: hexane to hexane/ Et_2O (1:1). Isolated as a white solid. Yield: 24%. Mp (Et_2O) = 119 °C. Rf [hexane / Et_2O (1:1)] = 0.50. ^1H NMR (500 MHz, CDCl_3) δ 8.35 – 8.27 (m, 1H), 7.84 – 7.78 (m, 1H), 7.46 – 7.38 (m, 3H), 7.38 – 7.29 (m, 3H), 4.42 (m, 1H), 3.88 (s, 3H), 3.73 (m, 1H), 2.67 (m, 2H), 2.42 (m, 1H), 2.17 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 165.7 (quat), 145.9 (quat), 138.7 (quat), 135.5 (quat), 132.2 (CH), 130.9 (quat), 129.7 (CH), 128.6 (CH), 127.1 (quat), 126.1 (CH), 122.7 (CH), 122.4 (CH), 121.8 (CH), 109.0 (CH), 103.3 (quat), 50.8 (CH_3), 40.8 (CH_2), 31.2 (CH_2), 30.5 (CH_2). HRMS (ES^+) calcd. for $(\text{M}+\text{H})^+ \text{C}_{19}\text{H}_{18}\text{NO}_2$: 292.1332; found 292.1334.

6,7-Dihydro-5H-benzo[3,4]azepino[1,2-a]indole-13-carbonitrile, (337).

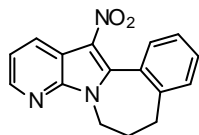


Prepared according to the general procedure C using compound **335** (52 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol), $\text{Cu}(\text{OAc})_2$ (109.0 mg, 0.6 mmol) and anhydrous

DMA (1 mL). Column system: hexane to hexane/ Et_2O (2:3). Isolated as a white solid. Yield: 79%. Mp (Et_2O) = 119 °C. Rf [hexane / Et_2O (1:1)] = 0.37. ^1H NMR (500 MHz, CDCl_3) δ 7.91 – 7.79 (m, 2H), 7.53 – 7.43 (m, 3H), 7.42 – 7.30 (m, 3H), 4.15 (t, $J = 6.7$ Hz, 2H), 2.73 (t, $J = 7.1$ Hz, 2H), 2.40 (p, $J = 6.9$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 147.8 (quat), 138.6 (quat), 135.6 (quat), 130.4 (CH), 129.7 (CH), 129.7 (quat), 129.5 (CH), 127.9 (quat), 127.6 (CH), 123.7 (CH), 122.1 (CH),

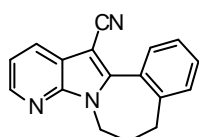
119.8 (CH), 116.7 (quat), 109.7 (CH), 83.5 (quat), 41.7 (CH₂), 31.1 (CH₂), 30.6 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₈H₁₅N₂: 259.1230; found 259.1231.

12-Nitro-6,7-dihydro-5H-7a,8-diaza-dibenzo[a,e]azulene, (338). Prepared



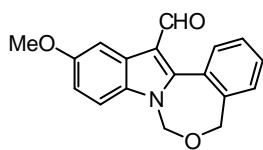
according to the general procedure C using compound **336** (56.2 mg, 0.2 mmol), K₂CO₃ (28.0 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Cu(OAc)₂ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 95%. Mp (Et₂O) = 168 °C. R_f [DCM] = 0.28. ¹H NMR (500 MHz, CDCl₃) δ 8.66 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.44 (d, *J* = 4.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.47 (tdd, *J* = 15.1, 10.7, 4.3 Hz, 2H), 7.37 (m, 2H), 5.13 (m, 1H), 3.48 (m, 1H), 2.77 (m, 1H), 2.60 (m, 1H), 2.49 (m, 1H), 2.22 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 145.4 (CH), 144.6 (quat), 142.3 (quat), 139.5 (quat), 132.1 (CH), 131.2 (CH), 130.0 (CH), 129.1 (CH), 127.9 (quat), 126.6 (CH), 122.9 (quat), 120.1 (CH), 115.0 (quat), 39.4 (CH₂), 31.4 (CH₂), 30.4 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₆H₁₄N₃O₂: 280.1081; found 280.1077.

6,7-Dihydro-5H-7a,8-diaza-dibenzo[a,e]azulene-12-carbonitrile, (343). Prepared



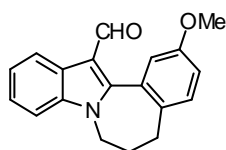
according to the general procedure C using compound **342** (52 mg, 0.2 mmol), K₂CO₃ (28.0 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Cu(OAc)₂ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 87%. Mp (Et₂O) = 144 °C. R_f [hexane / Et₂O (3:7)] = 0.48. ¹H NMR (500 MHz, CDCl₃) δ 8.44 (s, 1H), 8.11 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.95 – 7.77 (m, 1H), 7.49 (dd, *J* = 5.2, 3.7 Hz, 2H), 7.40 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.34 – 7.24 (m, 1H), 4.37 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 7.1 Hz, 2H), 2.42 (p, *J* = 6.9 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 148.6 (quat), 146.6 (quat), 144.7 (CH), 139.0 (quat), 130.8 (CH), 129.9 (CH), 129.5 (CH), 129.1 (quat), 127.9 (CH), 127.6 (CH), 120.7 (quat), 118.3 (CH), 81.4 (quat), 39.7 (CH₂), 30.9 (CH₂), 30.7 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₇H₁₄N₃: 260.1182; found 260.1185.

10-Methoxy-5H-6-oxa-7a-aza-dibenzo[a,e]azulene-12-carbaldehyde, (349).



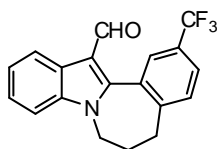
Prepared according to the general procedure C using compound **348** (59 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/ Et_2O (2:8). Isolated as a white solid. Yield: 65%. Mp (Et_2O) = 148 °C. Rf [hexane / Et_2O (2:8)] = 0.46. 1H NMR (500 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.84 – 7.72 (m, 1H), 7.68 – 7.58 (m, 2H), 7.56 (d, J = 6.8 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.04 (dd, J = 8.9, 2.5 Hz, 1H), 5.45 (s, 2H), 4.62 (s, 2H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.2 (quat), 157.1 (quat), 149.4 (quat), 134.2 (quat), 130.9 (CH), 130.9 (CH), 130.8 (CH), 130.5 (quat), 130.4 (quat), 129.7 (CH), 126.5 (quat), 115.1 (CH), 114.3 (quat), 110.1 (CH), 103.6 (CH), 69.7 (CH_2), 68.1 (CH_2), 55.9 (CH_3). HRMS (ES^+) cald. for $(M+H)^+$ $C_{18}H_{16}NO_3$: 294.1125; found 294.1126.

2-Methoxy-6,7- dihydro-5H- benzo [3,4] azepino [1,2-a] indole-13-carbaldehyde, (353).



Prepared according to the general procedure C using compound **350** (58.6 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/ Et_2O (2:8). Isolated as a white solid. Yield: 60%. Mp (Et_2O) = 144 °C. Rf [Et_2O /hexane (7:3)] = 0.52. 1H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.51 (dd, J = 6.7, 1.7 Hz, 1H), 7.44 (dd, J = 7.0, 1.5 Hz, 1H), 7.38 (dtd, J = 14.0, 7.0, 1.4 Hz, 2H), 7.31 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 2.7 Hz, 1H), 7.03 (dd, J = 8.3, 2.7 Hz, 1H), 4.45 (bs, 1H), 3.89 (s, 3H), 3.82 (bs, 1H), 2.73 (bs, 1H), 2.60 (bs, 1H), 2.47 (bs, 1H), 2.22 (bs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.2 (quat), 158.5 (quat), 150.6 (quat), 136.1 (quat), 131.3 (quat), 130.6 (CH), 130.3 (quat), 125.6 (quat), 123.9 (CH), 123.0 (CH), 122.6 (CH), 117.0 (CH), 115.7 (CH), 114.1 (quat), 109.0 (CH), 55.6 (CH_3), 41.1 (CH_2), 31.3 (CH_2), 29.6 (CH_2). HRMS (ES^+) cald. for $(M+H)^+$ $C_{19}H_{18}NO_2$: 292.1332; found 292.1331.

2-Trifluoromethyl-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-13-

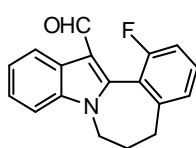


carbaldehyde, (354). Prepared according to the general procedure

C using compound **351** (66.2 mg, 0.2 mmol), K₂CO₃ (28.0 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Cu(OAc)₂ (109.0 mg,

0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/Et₂O (2:8). Isolated as a white solid. Yield: 80%. Mp (Et₂O) = 158 °C. Rf [Et₂O/hexane (7:3)] = 0.50. ¹H NMR (500 MHz, CDCl₃) δ 10.06 (s, 1H), 8.51 (d, *J* = 7.4 Hz, 1H), 7.88 (s, 1H), 7.76 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.34 (m, 3H), 4.51 (bs, 1H), 3.80 (bs, 1H), 2.88 (bs, 1H), 2.72 (bs, 1H), 2.57 (bs, 1H), 2.31 (bs, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 185.5 (quat), 148.4 (quat), 143.4 (d, *J* = 0.8 Hz, quat), 136.1 (quat), 130.3 (quat), 130.3 (CH), 129.8 (q, *J* = 33.0 Hz, quat), 127.9 (q, *J* = 3.7 Hz, CH), 127.0 (q, *J* = 3.6 Hz, CH), 125.5 (quat), 124.4 (CH), 123.8 (d, *J* = 272.3 Hz, quat), 123.3 (CH), 122.6 (CH), 114.5 (quat), 109.1 (CH), 40.9 (CH₂), 31.0 (CH₂), 30.6 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₁₅NOF₃: 330.1100; found 330.1101.

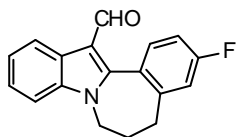
1-Fluoro-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-13-carbaldehyde,



(355a). Prepared according to the general procedure C using compound **352** (56.2 mg, 0.2 mmol), K₂CO₃ (28.0 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Cu(OAc)₂ (109.0 mg, 0.6 mmol)

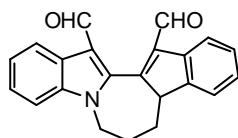
and anhydrous DMA (1 mL). Column system: hexane to hexane/Et₂O (1:1). Isolated as a white solid. Yield: 51%. Mp (Et₂O) = 139 °C. Rf [Et₂O/hexane (6:4)] = 0.39. ¹H NMR (500 MHz, CDCl₃) δ 10.02 (d, *J* = 5.4 Hz, 1H), 8.50 (dd, *J* = 6.1, 2.7 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.44 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.23 – 7.20 (m, 2H), 4.47 (dd, *J* = 14.6, 6.5 Hz, 1H), 3.81 (ddd, *J* = 14.3, 13.1, 5.7 Hz, 1H), 2.89 – 2.72 (m, 1H), 2.59 – 2.45 (m, 2H), 2.32 – 2.11 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 186.2 (d, *J* = 6.0 Hz, quat), 159.5 (d, *J* = 250.6 Hz, quat), 142.2 (quat), 141.9 (d, *J* = 0.8 Hz, quat), 136.4 (quat), 131.9 (d, *J* = 8.8 Hz, CH), 125.5 (quat), 125.2 (d, *J* = 3.2 Hz, CH), 123.9 (CH), 123.0 (CH), 122.6 (CH), 117.5 (d, *J* = 14.0 Hz, quat), 114.9 (d, *J* = 22.6 Hz, CH), 114.7 (d, *J* = 1.5 Hz, quat), 109.0 (CH), 40.8 (CH₂), 31.0 (CH₂), 30.4 (d, *J* = 2.2 Hz, CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₈H₁₅NOF: 280.1132; found 280.1132.

2-Fluoro-6,7-dihydro-5H-benzo[3,4]azepino[1,2-a]indole-13-carbaldehyde,



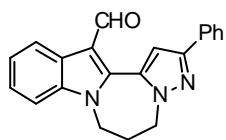
(**355b**). Prepared according to the general procedure C using compound **352** (56.2 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to hexane/ Et_2O (1:1). Isolated as a white solid. Yield: 13%. Mp (Et_2O) = 179 °C. Rf [Et_2O /hexane (6:4)] = 0.48. 1H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.50 (dd, J = 6.8, 1.7 Hz, 1H), 7.62 (dd, J = 8.3, 5.6 Hz, 1H), 7.44 (dd, J = 7.1, 1.6 Hz, 1H), 7.39 (dtd, J = 13.9, 6.9, 1.5 Hz, 2H), 7.22 – 7.11 (m, 2H), 4.47 (bs, 1H), 3.80 (bs, 1H), 2.77 – 2.71 (m, 2H), 2.53 (bs, 1H), 2.29 (bs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.8 (quat), 163.8 (d, J = 251.3 Hz, quat), 149.5 (quat), 142.0 (d, J = 8.1 Hz, quat), 136.0 (quat), 133.3 (d, J = 8.8 Hz, CH), 125.6 – 125.5 (m, quat), 124.0 (CH), 123.1 (CH), 122.5 (CH), 116.9 (d, J = 21.8 Hz, CH), 114.2 (quat), 114.1 (d, J = 21.6 Hz, CH), 109.0 (CH), 40.9 (CH_2), 31.0 (CH_2), 30.7 (d, J = 1.2 Hz, CH_2). HRMS (ES^+) calcd. for $(M+H)^+$ $C_{18}H_{15}NOF$: 280.1132; found 280.1132.

7,8-Dihydro-6H-[1,4]diazepino[1,2-a;4,3-a']diindole-14,15-dicarbaldehyde,



(**360a**). Prepared according to the general procedure C using compound **359a** (66.0 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to DCM/ $EtOAc$ (9:1). Isolated as a white solid. Yield: 91%. Mp (Et_2O) = 276 °C. Rf [DCM/ $EtOAc$ (95:05)] = 0.54. 1H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 2H), 8.52 (d, J = 8.0 Hz, 2H), 7.54 – 7.47 (m, 4H), 7.44 – 7.33 (m, 2H), 4.80 – 4.61 (m, 2H), 4.08 – 3.86 (m, 2H), 2.74 – 2.51 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.6 (2 quat), 136.9 (2 quat), 136.3 (2 quat), 125.7 (2 CH), 125.4 (2 quat), 123.8 (2 CH), 122.9 (2 CH), 118.4 (2 quat), 109.3 (2 CH), 40.8 ($2CH_2$), 29.6 (CH_2). HRMS (ES^+) calcd. for $(M+H)^+$ $C_{21}H_{17}NO$: 329.1285; found 329.1282.

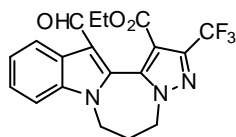
Compound, (360b). Prepared according to the general procedure C using compound



359b (65.8 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to

hexane/ Et_2O (2:8). Isolated as a white solid. Yield: 84%. Mp (Et_2O) = 218 °C. Rf [Et_2O /hexane (8:2)] = 0.34. 1H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.95 – 7.84 (m, 2H), 7.52 – 7.35 (m, 6H), 7.04 (s, 1H), 4.48 (t, J = 6.7 Hz, 2H), 4.31 (t, J = 6.7 Hz, 2H), 2.64 (p, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.1 (quat), 151.4 (quat), 138.9 (quat), 136.9 (quat), 133.3 (quat), 132.4 (quat), 128.9 (2CH), 128.3 (CH), 125.6 (2CH), 125.3 (quat), 124.8 (CH), 123.5 (CH), 122.7 (CH), 115.5 (quat), 109.2 (CH), 107.0 (CH), 47.9 (CH_2), 41.2 (CH_2), 30.0 (CH_2). HRMS (ES^+) cald. for $(M+H)^+$ $C_{21}H_{18}N_3O$: 328.1444; found 328.1445.

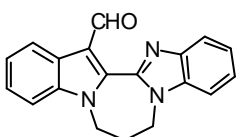
Compound, (360c). Prepared according to the general procedure C using compound



359c (78.6 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). Column system: hexane to

hexane/ Et_2O (2:8). Isolated as a white solid. Yield: 43%. Mp (Et_2O) = 120 °C. Rf [Et_2O /hexane (8:2)] = 0.45. 1H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.51 – 7.36 (m, 3H), 4.77 – 4.55 (m, 2H), 4.38 – 4.19 (m, 2H), 4.12 – 3.98 (m, 1H), 3.98 – 3.77 (m, 1H), 2.75 – 2.47 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.2 (quat), 160.2 (quat), 142.3 (q, J = 38.5 Hz, quat), 136.6 (quat), 136.5 (quat), 133.0 (quat), 125.4 (CH), 125.2 (quat), 123.7 (CH), 123.0 (CH), 120.3 (d, J = 270.0 Hz, quat), 116.9 (quat), 113.8 (quat), 109.2 (CH), 61.7 (CH_2), 48.5 (CH_2), 40.3 (CH_2), 29.9 (CH_2), 13.8 (CH_3). HRMS (ES^+) cald. for $(M+H)^+$ $C_{19}H_{17}N_3O_3F_3$: 392.1217; found 392.1215.

Compound, (360d). Prepared according to the general procedure C using compound



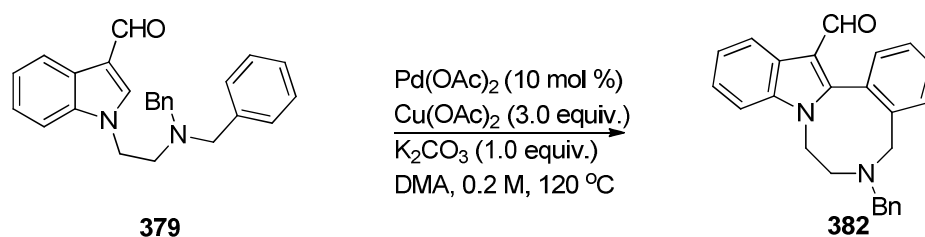
359d (60.6 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL) at 140 °C for 3 hr. Column system:

hexane to DCM/ $EtOAc$ (6:4). Isolated as a white solid. Yield: 62%. Mp (Et_2O) = 216

°C. Rf [DCM/EtOAc (1:1)] = 0.62. ¹H NMR (500 MHz, CDCl₃) δ 10.67 (s, 1H), 8.55 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.55 – 7.33 (m, 6H), 4.47 – 4.31 (m, 4H), 2.67 (p, *J* = 6.6 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 187.8 (quat), 143.6 (quat), 138.0 (quat), 137.0 (quat), 125.4 (quat), 125.2 (quat), 124.3 (CH), 123.6 (CH), 123.4 (CH), 123.2 (quat), 120.9 (CH), 118.1 (quat), 109.3 (CH), 109.3 (CH), 41.6 (CH₂), 41.0 (CH₂), 29.3 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₉H₁₆N₃O: 302.1288; found 302.1291.

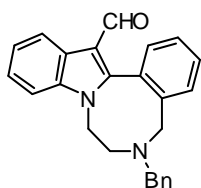
Compound, (361). Isolated as by-product while making compound **360d**. Yellow oil. Column system: hexane to DCM/EtOAc (6:4). Rf [DCM/EtOAc (1:1)] = 0.70. ¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, *J* = 4.6 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.59 (s, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.20 (t, *J* = 7.4 Hz, 1H), 4.56 – 4.45 (m, 2H), 4.45 – 4.36 (m, 2H), 2.64 (dt, *J* = 12.0, 6.1 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 146.9 (quat), 143.0 (quat), 138.3 (quat), 135.6 (quat), 130.2 (quat), 128.4 (CH), 127.7 (quat), 123.5 (CH), 122.9 (CH), 121.9 (CH), 120.6 (CH), 119.6 (CH), 109.4 (CH), 109.1 (CH), 107.1 (CH), 43.7 (CH₂), 43.7 (CH₂), 28.0 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₈H₁₆N₃: 274.1338; found 274.1335.

Procedure D: identical as procedure C, except that reactions were carried out at 120 °C instead of 90 °C.



Scheme 2.88. Representative procedure for 8-membered rings synthesis.

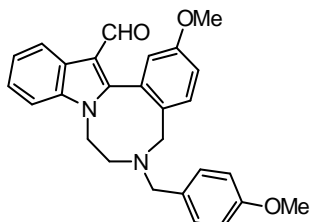
Compound, (382). Prepared according to the general procedure D using compound



379 (73.6 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL) at 120 °C for 16 hr. Column system: hexane to hexane/Et₂O (2:8). Isolated as a whitish solid. Yield:

60%. Mp (Et₂O) = 74 °C. Rf [Et₂O/hexane (7:3)] = 0.50. ¹H NMR (500 MHz, CDCl₃) δ 9.84 (s, 1H), 8.50 (dd, *J* = 5.7, 2.5 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.45 – 7.28 (m, 9H), 7.18 (d, *J* = 7.6 Hz, 1H), 4.35 (dd, *J* = 15.3, 5.1 Hz, 1H), 3.97 – 3.76 (m, 3H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.31 (dd, *J* = 13.2, 5.5 Hz, 1H), 3.06 (d, *J* = 14.1 Hz, 1H), 2.80 (dd, *J* = 13.0, 10.1 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 186.7 (quat), 151.0 (quat), 140.6 (quat), 138.6 (quat), 136.1 (quat), 132.2 (CH), 131.4 (CH), 130.6 (CH), 129.2 (2 CH), 128.5 (2 CH), 127.6 (quat), 127.6 (CH), 127.3 (CH), 125.7 (quat), 124.0 (CH), 123.4 (CH), 122.4 (CH), 114.8 (quat), 109.5 (CH), 61.8 (CH₂), 55.9 (CH₂), 54.9 (CH₂), 43.3 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₅H₂₃N₂O: 367.1805; found 367.1804.

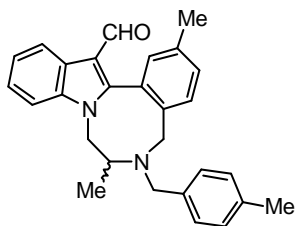
Compound, (389). Prepared according to the general procedure D using compound



383 (85.6 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL) at 120 °C for 16 hr. Column system: hexane to hexane/Et₂O (2:8). Isolated as an yellow oil. Yield: 55%. Rf [DCM] = 0.23. ¹H NMR

(500 MHz, CDCl₃) δ 9.91 (s, 1H), 8.51 (dd, *J* = 5.3, 3.1 Hz, 1H), 7.42 – 7.39 (m, 3H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.18 – 6.99 (m, 3H), 6.93 (d, *J* = 8.6 Hz, 2H), 4.36 (dd, *J* = 15.3, 5.3 Hz, 1H), 3.92 (dd, *J* = 15.4, 9.9 Hz, 1H), 3.86 (bs, 6H), 3.81 (dd, *J* = 17.5, 7.8 Hz, 2H), 3.49 (d, *J* = 13.4 Hz, 1H), 3.32 (dd, *J* = 13.2, 5.5 Hz, 1H), 2.95 (d, *J* = 14.1 Hz, 1H), 2.77 (dd, *J* = 13.1, 10.0 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 186.6 (quat), 159.0 (quat), 158.3 (quat), 150.8 (quat), 136.0 (quat), 132.8 (quat), 132.7 (CH), 130.6 (quat), 130.4 (2 CH), 128.6 (quat), 125.6 (quat), 124.0 (CH), 123.4 (CH), 122.4 (CH), 116.7 (CH), 116.6 (CH), 114.6 (quat), 113.8 (2 CH), 109.5 (CH), 60.9 (CH₂), 55.5 (CH₃), 55.3 (CH₃), 54.8 (CH₂), 54.8 (CH₂), 43.3 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₇H₂₇N₂O₃: 427.2016; found 427.2021.

Compound, (390). Prepared according to the general procedure D using compound

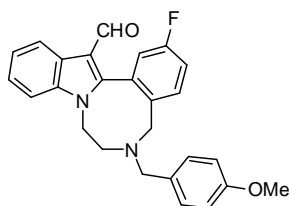


384 (82.1 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL) at 120 °C for 16 hr. Column system: hexane to DCM. Isolated as a yellow oil.

Yield: 51%. R_f [DCM] = 0.32. 1H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H), 9.78 (s, 1H), 8.57 – 8.50 (m, 2H), 7.45 – 7.23 (m, 12H), 7.21 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.9 Hz, 2H), 6.90 (d, J = 7.9 Hz, 2H), 4.27 (dd, J = 15.1, 5.0 Hz, 1H), 4.16 (dd, J = 14.9, 3.4 Hz, 1H), 4.07 – 3.91 (m, 3H), 3.81 – 3.72 (m, 4H), 3.57 – 3.51 (m, 1H), 3.43 (d, J = 15.8 Hz, 1H), 3.36 (dd, J = 12.8, 8.7 Hz, 2H), 3.15 – 3.03 (m, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H), 2.31 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.2 (quat), 186.9 (quat), 152.9 (quat), 152.0 (quat), 138.5 (quat), 138.0 (quat), 137.0 (quat), 136.9 (quat), 136.7 (quat), 136.5 (quat), 136.2 (quat), 136.1 (quat), 135.9 (quat), 135.7 (quat), 134.2 (CH), 133.7 (CH), 132.0 (CH), 130.9 (CH), 130.8 (CH), 129.5 (CH), 129.2 (2 CH), 128.9 (2 CH), 128.6 (2 CH), 128.5 (2 CH), 128.0 (quat), 126.8 (quat), 125.9 (quat), 125.6 (quat), 123.7 (CH), 123.7 (CH), 123.2 (CH), 123.1 (CH), 122.4 (CH), 122.3 (CH), 115.4 (quat), 114.5 (quat), 110.6 (CH), 109.4 (CH), 58.5 (CH_2), 57.0 (CH_2), 55.9 (CH), 53.8 (CH), 53.1 (CH_2), 48.9 (CH_2), 48.7 (CH_2), 45.6 (CH_2), 21.2 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 15.6 (CH_3), 15.3 (CH_3). HRMS (ES^+) cald. for $(M+H)^+$ $C_{28}H_{29}N_2O$: 409.2274; found 409.2277.

Compounds **391a** and **391b** could not be separated by silica gel column chromatography. Purification by preparative TLC was used to isolate the two isomers.

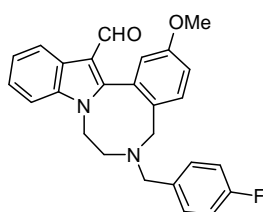
Compound, (391a). Prepared according to the general procedure D using compound



385 (51 mg, 0.122 mmol), K_2CO_3 (17.0 mg, 0.122 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), $Cu(OAc)_2$ (67.0 mg, 0.367 mmol) and anhydrous DMA (800 μ L) at 120 °C for 16 hr.

Column system: hexane to hexane/Et₂O (2:8). Isolated as a yellow oil. R_f [Et₂O/Hexane (7:3)] = 0.47. ¹H NMR (500 MHz, CDCl₃) δ 9.89 (s, 1H), 8.59 – 8.41 (m, 1H), 7.47 – 7.37 (m, 3H), 7.28 (d, *J* = 7.0 Hz, 2H), 7.22 (ddd, *J* = 20.6, 8.5, 2.7 Hz, 2H), 7.12 (dd, *J* = 8.5, 5.6 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 4.40 (dd, *J* = 15.4, 5.1 Hz, 1H), 3.97 – 3.76 (m, 6H), 3.49 (d, *J* = 13.0 Hz, 1H), 3.33 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.96 (d, *J* = 14.1 Hz, 1H), 2.79 (dd, *J* = 13.0, 9.9 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 186.1 (quat), 161.1 (d, *J* = 248.4 Hz, quat), 159.1 (quat), 149.1 (d, *J* = 2.0 Hz, quat), 136.8 (d, *J* = 3.5 Hz, quat), 136.0 (quat), 133.2 (d, *J* = 8.3 Hz, CH), 130.4 (2CH), 130.3 (quat), 129.3 (d, *J* = 8.4 Hz, quat), 125.6 (quat), 124.2 (CH), 123.6 (CH), 122.5 (CH), 118.5 (d, *J* = 22.5 Hz, CH), 117.6 (d, *J* = 20.9 Hz, CH), 114.9 (quat), 113.9 (2CH), 109.5 (CH), 61.2 (CH₂), 55.3 (CH₃), 54.8 (CH₂), 54.6 (CH₂), 43.5 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₆H₂₄N₂O₂F: 415.1816; found 415.1816.

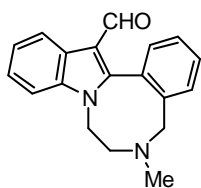
Compound, (391b). Prepared according to the general procedure D using compound



385 (51 mg, 0.122 mmol), K₂CO₃ (17.0 mg, 0.122 mmol), Pd(OAc)₂ (2.7 mg, 0.012 mmol), Cu(OAc)₂ (67.0 mg, 0.367 mmol) and anhydrous DMA (800 μL) at 120 °C for 16 hr. Column system: hexane to hexane/Et₂O (2:8). Isolated as a yellow oil. R_f [Et₂O/Hexane (7:3)] = 0.45. ¹H NMR (500

MHz, CDCl₃) δ 9.91 (s, 1H), 8.62 – 8.36 (m, 1H), 7.45 – 7.37 (m, 3H), 7.35 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.12 – 7.02 (m, 5H), 4.37 (dd, *J* = 15.3, 5.1 Hz, 1H), 3.98 – 3.82 (m, 5H), 3.77 (d, *J* = 14.2 Hz, 1H), 3.54 (d, *J* = 13.3 Hz, 1H), 3.30 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.02 (d, *J* = 14.2 Hz, 1H), 2.80 (dd, *J* = 13.1, 9.9 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 186.6 (quat), 162.2 (d, *J* = 245.6 Hz, quat), 158.4 (quat), 150.7 (quat), 136.0 (quat), 134.3 (d, *J* = 3.1 Hz, quat), 132.5 (quat), 132.5 (CH), 130.7 (d, *J* = 7.9 Hz, 2CH), 128.7 (quat), 125.6 (quat), 124.0 (CH), 123.5 (CH), 122.5 (CH), 116.9 (CH), 116.6 (CH), 115.3 (d, *J* = 21.3 Hz, 2CH), 114.7 (quat), 109.4 (CH), 60.6 (CH₂), 55.5 (CH₃), 55.1 (CH₂), 54.8 (CH₂), 43.2 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₂₆H₂₄N₂O₂F: 415.1816; found 415.1816.

Compound, (392). Prepared according to the general procedure D using compound

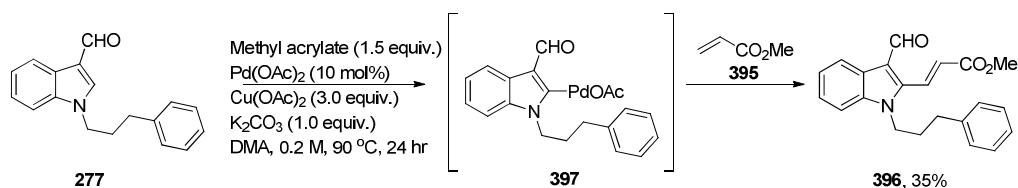


386 (58.4 mg, 0.2 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL) at 120 °C for 16 hr. Column system: hexane to hexane/EtOAc (2:3). Isolated as an yellow oil. Yield:

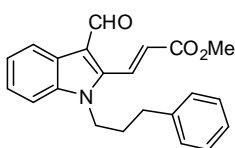
37%. Rf [EtOAc/Hexane (1:1)] = 0.32. 1H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.58 – 8.30 (m, 1H), 7.61 – 7.55 (m, 1H), 7.53 (d, J = 7.7 Hz, 2H), 7.45 (td, J = 7.4, 1.4 Hz, 1H), 7.42 – 7.35 (m, 3H), 4.31 (dd, J = 15.4, 5.3 Hz, 1H), 3.82 (dd, J = 15.5, 10.0 Hz, 1H), 3.73 (d, J = 13.9 Hz, 1H), 3.25 (dd, J = 13.5, 5.7 Hz, 1H), 3.14 (d, J = 13.9 Hz, 1H), 2.78 (dd, J = 13.5, 9.8 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6 (quat), 150.6 (quat), 139.8 (quat), 136.0 (quat), 132.2 (CH), 131.9 (CH), 130.7 (CH), 127.7 (quat), 127.5 (CH), 125.6 (quat), 124.0 (CH), 123.5 (CH), 122.4 (CH), 114.8 (quat), 109.4 (CH), 58.4 (CH_2), 56.7 (CH_2), 45.6 (CH_3), 42.7 (CH_2).). HRMS (ES^+) calcd. for $(M+H)^+$ $C_{19}H_{19}N_2O$: 291.1492; found 291.1491.

2.5.5 Mechanistic studies:

2.5.5.1 Trapping experiment



(E)-3-[3-Formyl-1-(3-phenyl-propyl)-1H-indol-2-yl]-acrylic acid methyl ester, (**396**).

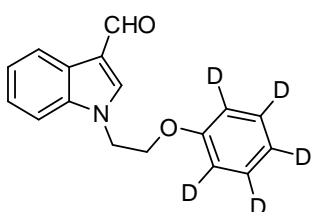


A 5 mL microwave vial was charged with 1-(3-Phenyl-propyl)-1H-indole-3-carbaldehyde **277**. (53.0 mg, 0.20 mmol), methyl acrylate (27.0 uL, 0.30 mmol), K₂CO₃ (28.0 mg, 0.20 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Cu(OAc)₂ (109.0 mg, 0.6 mmol) and anhydrous DMA (1 mL). The tube was then sealed with a serum cap and the reaction was flushed with nitrogen. The reaction mixture was allowed to stir at room temperature until the starting material completely dissolved before being placed into a pre-thermostated carrousel at 90 °C for 16 hr. The mixture was allowed to cool down and directly poured on top of a long silica gel column chromatography. The product was eluted with a mixture hexane/Et₂O (75:35). Pure **396** was obtained in 35% yield as a yellow solid. Mp (Et₂O) = 93 °C. R_f [hexane / Et₂O (4:6)] = 0.50. ¹H NMR (500 MHz, CDCl₃) δ 10.19 (s, 1H), 8.42 (dd, *J* = 6.8, 1.9 Hz, 1H), 7.85 (d, *J* = 15.9 Hz, 1H), 7.39 - 7.33 (m, 4H), 7.30 - 7.23 (m, 2H), 7.19 (d, *J* = 7.2 Hz, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 4.34 - 4.16 (m, 2H), 3.90 (s, 3H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.28 - 2.11 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 185.0 (quat), 165.8 (quat), 142.2 (quat), 140.0 (quat), 137.1 (quat), 130.2 (CH), 128.7 (2 CH), 128.3 (2 CH), 127.9 (CH), 126.5 (CH), 125.9 (quat), 125.2 (CH), 123.6 (CH), 122.4 (CH), 117.0 (quat), 110.0 (CH), 52.3 (CH₃), 43.8 (CH₂), 32.9 (CH₂), 31.0 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₂₂H₂₂NO₃: 348.1594; found 348.1593.

2.5.5.2 Kinetic Isotope Effects (KIEs)

1-(2-Phenoxy-ethyl)-1H-(2deutero)indole-3-carbaldehyde, (312-D). Following general procedure A, using 2-deuteroindole-3-carboxyaldehyde (226 mg, 1.55 mmol), NaH (68 mg, 1.70 mmol, 60 wt% in mineral oil) and (2-bromo-ethoxy)-benzene (374 mg, 1.90 mmol). Yellow solid; yield: 74%. Mp (Et₂O) = 115 °C. Rf [hexane/DCM (7:3)] = 0.60. ¹H NMR (500 MHz, CDCl₃) δ 10.06 (s, 1H), 8.36 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.38 (ddt, *J* = 13.4, 7.2, 3.7 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.03 – 6.96 (m, 1H), 6.93 – 6.82 (m, 2H), 4.61 (t, *J* = 5.2 Hz, 2H), 4.37 (t, *J* = 5.2 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.6 (quat), 157.8 (quat), 138.7 (t, *J* = 25.2 Hz, CD), 137.2 (quat), 129.7 (2CH), 125.4 (quat), 124.1 (CH), 123.0 (CH), 122.3 (CH), 121.7 (CH), 118.4 (quat), 114.5 (2CH), 109.8 (CH), 66.0 (CH₂), 46.5 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₇H₁₅²H₁NO₂: 267.1238; found 267.1238.

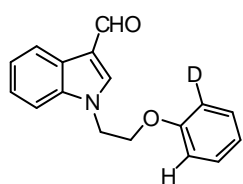
1-(2-d₅Phenoxy-ethyl)-1H-indole-3-carbaldehyde, (312-D₅). Following general



procedure A, using indole-3-carboxyaldehyde (429 mg, 2.95 mmol), NaH (118 mg, 2.95 mmol, 60 wt% in mineral oil) and (2-bromo-ethoxy)-benzene-d₅ (610 mg, 2.96 mmol). Column system: hexane to hexane/DCM (6:4).

Yellow solid; yield: 45%. Mp (Et₂O) = 122 °C. Rf [hexane/DCM (7:3)] = 0.61. ¹H NMR (500 MHz, CDCl₃) δ 10.05 (s, 1H), 8.36 (d, *J* = 7.7 Hz, 1H), 7.88 (s, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.32 (m, 2H), 4.59 (t, *J* = 5.2 Hz, 2H), 4.35 (t, *J* = 5.2 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.7 (quat), 157.8 (quat), 139.1 (CH), 137.3 (quat), 129.2 (t, *J* = 24.3 Hz, 2CD), 125.4 (quat), 124.1 (CH), 123.0 (CH), 122.3 (CH), 121.1 (t, *J* = 24.8 Hz, CD), 118.6 (quat), 114.0 (t, *J* = 24.3 Hz, 2CD), 109.8 (CH), 66.0 (CH₂), 46.5 (CH₂). HRMS (ES⁺) calcd. for (M+H)⁺ C₁₇H₁₁²H₅NO₂: 271.1489; found 271.1489.

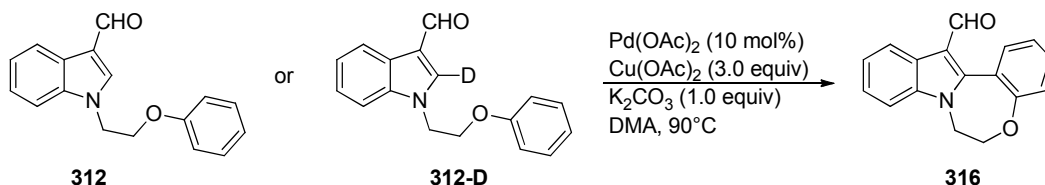
1-(2-*o*-deuteriophenoxy-ethyl)-1*H*-indole-3-carbaldehyde, (312-H/D). Following



general procedure A, using indole-3-carboxyaldehyde (174.0 mg, 1.2 mmol), NaH (48 mg, 1.2 mmol, 60 wt% in mineral oil) and (2-bromo-ethoxy)-2-deuteriobenzene¹⁵² (197 mg, 1.0 mmol). Column system: hexane to hexane/DCM (6:4). White

solid; yield: 75%. Mp (Et₂O) = 113 °C. R_f [hexane/Et₂O (3:7)] = 0.38. ¹H NMR (500 MHz, CDCl₃) δ 10.05 (s, 1H), 8.36 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.89 (s, 1H), 7.49 – 7.43 (m, 1H), 7.43 – 7.33 (m, 2H), 7.33 – 7.26 (m, 2H), 7.00 (td, *J* = 7.4, 0.9 Hz, 1H), 6.87 (dd, *J* = 8.7, 0.8 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 2H), 4.35 (t, *J* = 5.2 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 184.7 (quat), 157.8 (quat), 139.2 (CH), 137.2 (quat), 129.7 (CH), 129.6 (CH), 125.4 (quat), 124.1 (CH), 123.0 (CH), 122.3 (CH), 121.6 (CH), 118.5 (quat), 114.5 (CH), 114.2 (t, *J* = 24.3 Hz, CD), 109.8 (CH), 66.0 (CH₂), 46.5 (CH₂). HRMS (ES⁺) cald. for (M+H)⁺ C₁₇H₁₅(²H₁)NO₂: 267.1238; found 267.1238.

2.5.5.2.1 Procedure for the determination of the intermolecular KIE at the indole C2 position.



General considerations. Reactions were run in 3 mL test tubes sealed with a screw cap. Each reaction in an individual vial represents a point within a kinetic run. Each reaction vial contained a constant concentration of oxidant, catalyst, base and substrate. The initial rate of the reaction was recorded by analysing the formation of the product over time at the beginning of the reaction. Duplicate experiments were performed in the same aluminium heating block pre-heated at 90 °C and at the desired time, reactions were stopped by freezing the reaction vials in an ice bath at 0 °C. A solution of methanol containing benzanilide as internal standard was used to quench the reactions and dilute the samples. Product formation was determined by

LCMS using peak area of mass spectrometry response (Single Ion Monitoring (SIM)) for the product versus SIM of the internal standard (benzanilide).

Method A. For each experiment, a 3 mL screw vial was loaded with Cu(OAc)₂ (27.2 mg, 0.15 mmol) and K₂CO₃ (6.9 mg, 0.05 mmol). Then 200 µL of a DMA solution containing the starting material (0.1M) was added to the vial, followed by 200 µL of a DMA solution of Pd(OAc)₂ (0.1 M). Each vial was sealed and heated at the same time using a pre-thermostated carrousel at 90 °C. At the appropriate time, reactions were quenched by freezing them into an ice bath for 15 minutes. Then 5 µL aliquots were taken out and diluted into 1 mL using a solution of benzanilide (0.1 mM) in methanol. Samples were analysed by LCMS and mass spectroscopy response of the product formation was recorded ($\text{SIM}_{\text{pdr}}/\text{SIM}_{\text{IS}} = f(t)$).

| Deutero indole | | | Proteo indole | | |
|----------------|------|------------------|---------------|------|------------------|
| Exp | Time | SIM(Pdr)/SIM(IS) | Exp | Time | SIM(Pdr)/SIM(IS) |
| 1 | 9 | 0,0119 | 1 | 9 | 0,0126 |
| 2 | 12 | 0,0113 | 2 | 12 | 0,0366 |
| 3 | 16 | 0,0114 | 3 | 16 | 0,0323 |
| 4 | 20 | 0,0179 | 4 | 20 | 0,0677 |
| 5 | 27 | 0,1050 | 5 | 27 | 0,2075 |
| 6 | 35 | 0,1698 | 6 | 35 | 0,4198 |
| 7 | 45 | 0,2618 | 7 | 45 | 0,6277 |
| 8 | 55 | 0,3480 | 8 | 55 | 0,8244 |
| 9 | 70 | 0,5279 | 9 | 70 | 1,0727 |
| 10 | 90 | 0,6539 | 10 | 90 | 1,2070 |

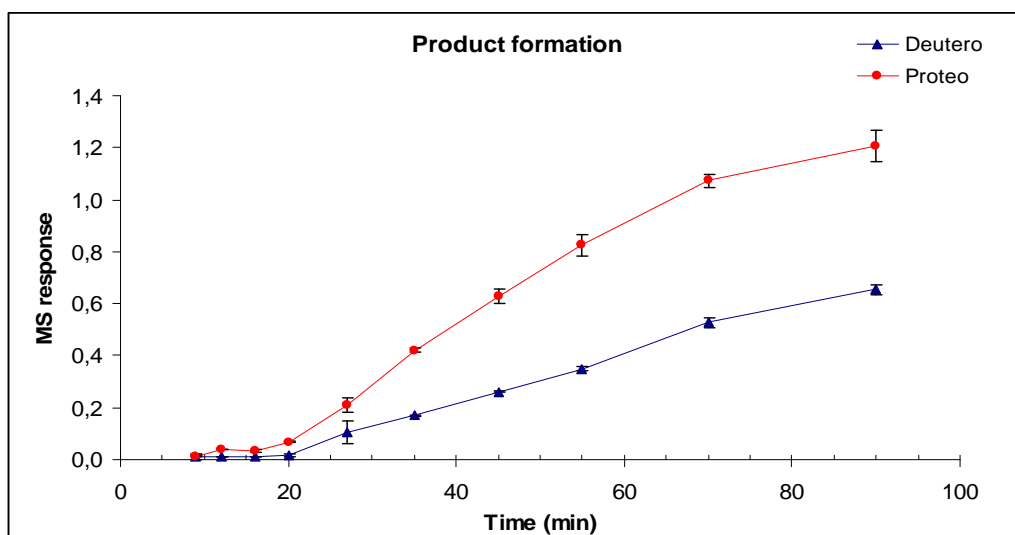


Figure 2.20. Method A: Product formation for proteo and deuterio substrates versus time.

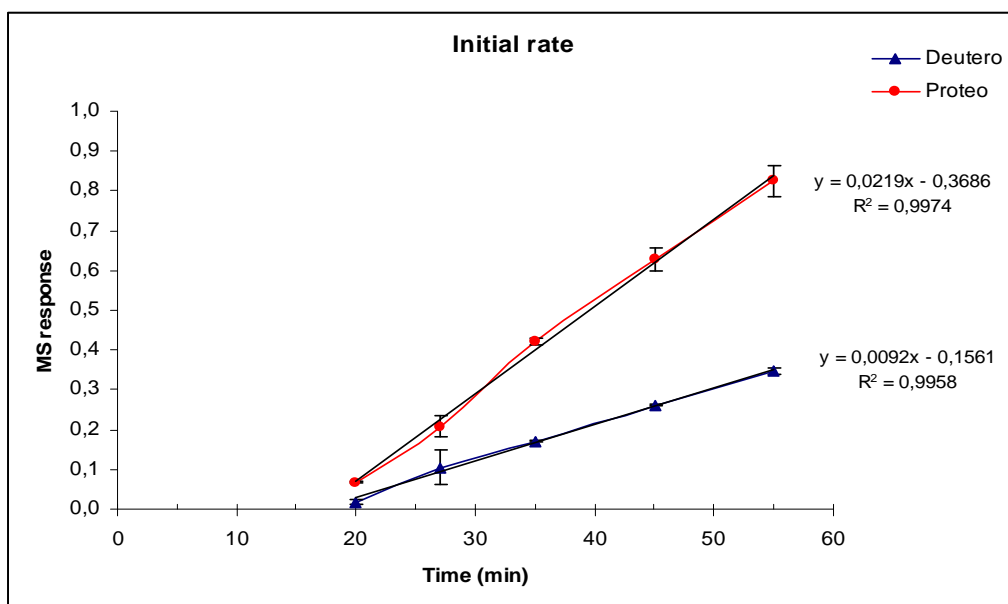


Figure 2.21. Method A: Initial rate of product formation for proteo and deuterio substrates.

$$\text{KIE: } k_H / k_D = 0.0219 / 0.0092 = 2.38$$

Method B:

General considerations. Method B is very similar to method A. The main difference is that the initial rates were determined by performing the reaction in a larger reaction vial and by taking aliquots from the same reaction mixture at desired amounts of time instead of having a reaction vial for each data point as in method A. Aliquots taken from the same reaction vessel were rapidly quenched by a methanolic solution of benzanilide used as internal standard. Method B afforded less standard deviation than method A. Experiments for both deuterated and non-deuterated substrates were conducted simultaneously in the same reaction block. The Initial rate for each substrate was determined from the average of two sets of trials.

Method B. A 5 mL microwave vial was charged with deuterated (or non-deuterated) indole (0.272 mmol), K₂CO₃ (41.5mg, 0.272 mmol), Pd(OAc)₂ (6.1 mg, 0.027 mmol), Cu(OAc)₂ (148.0 mg, 0.820 mmol) and anhydrous DMA (2 mL). The vial was then sealed with a serum cap and the reaction was flushed with nitrogen. The reaction mixture was allowed to stir at room temperature until the starting material completely dissolved before being placed into a pre-thermostated carousel at 90 °C. Aliquots (5 µL) were taken out at the desired time and diluted into 1 mL with a solution of benzanilide (0.1 mM) in methanol. Peak area of Single Ion Monitoring (SIM) for the product was recorded by LCMS versus SIM of the internal standard (benzanilide).

| Deutero indole | | | Proteo indole | | |
|----------------|------|------------------|---------------|------|------------------|
| Exp | Time | SIM(Pdr)/SIM(IS) | Exp | Time | SIM(Pdr)/SIM(IS) |
| 1 | 5 | 0,0055 | 1 | 5 | 0,0000 |
| 2 | 10 | 0,0144 | 2 | 10 | 0,0220 |
| 3 | 15 | 0,1654 | 3 | 15 | 0,2000 |
| 4 | 20 | 0,3846 | 4 | 20 | 0,7552 |
| 5 | 25 | 0,5501 | 5 | 25 | 1,2127 |
| 6 | 30 | 0,7414 | 6 | 30 | 1,6432 |
| 7 | 35 | 0,8250 | 7 | 35 | 1,8691 |
| 8 | 40 | 0,9041 | 8 | 40 | 2,0775 |
| 9 | 45 | 0,9313 | 9 | 45 | 2,1964 |
| 10 | 50 | 0,9764 | 10 | 50 | 2,3340 |
| 11 | 65 | 0,9898 | 11 | 65 | 2,5375 |

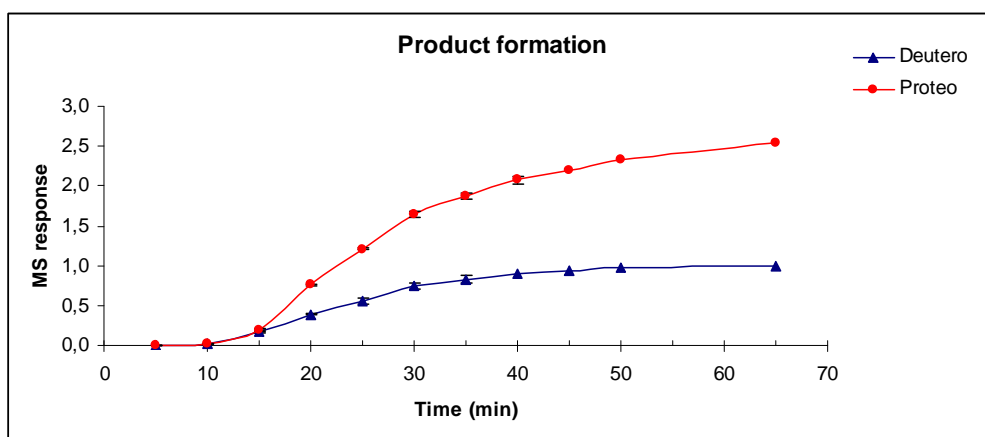


Figure 2.22. Method B: Product formation for proteo and deuterio substrates versus time.

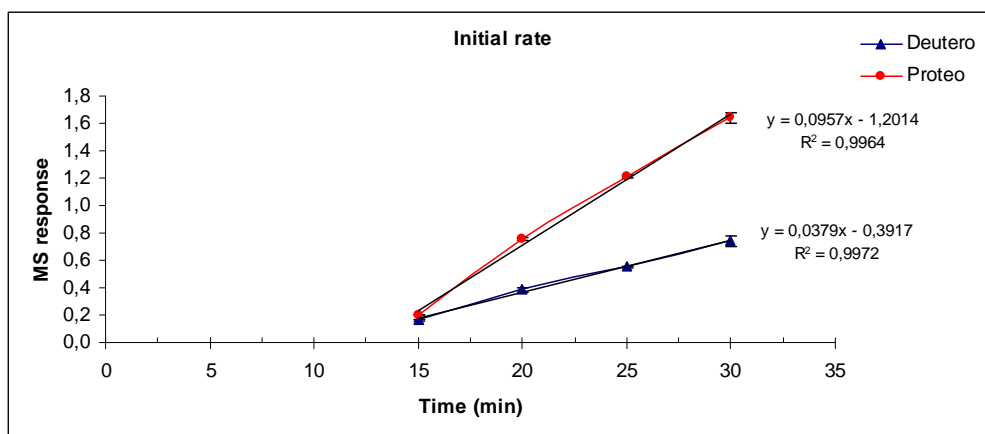
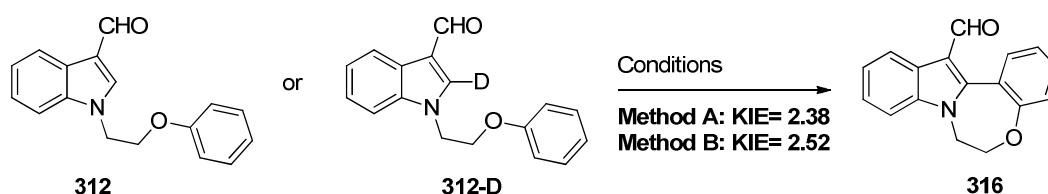


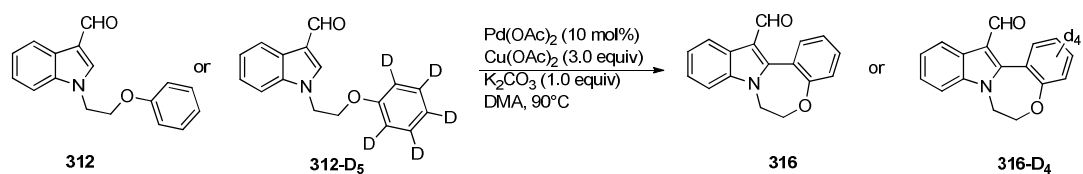
Figure 2.23. Method B: Initial rate of product formation for proteo and deuterio substrates.

$$\text{KIE: } k_{\text{H}} / k_{\text{D}} = 0.0957 / 0.0379 = 2.52$$

Summary:



2.5.5.2.2 Procedure for the determination of intermolecular KIE at the aryl position



Method A:

Method A as previously described was used to determine the initial rate of the reaction.

| Deutero (d ₅) indole | | | Proteo indole | | |
|----------------------------------|------|------------------|---------------|------|------------------|
| Exp | Time | SIM(Pdr)/SIM(IS) | Exp | Time | SIM(Pdr)/SIM(IS) |
| 1 | 9 | 0,0039 | 1 | 9 | 0,0126 |
| 2 | 12 | 0,0123 | 2 | 12 | 0,0366 |
| 3 | 16 | 0,0406 | 3 | 16 | 0,0323 |
| 4 | 20 | 0,0828 | 4 | 20 | 0,0677 |
| 5 | 27 | 0,1398 | 5 | 27 | 0,2075 |
| 6 | 35 | 0,2127 | 6 | 35 | 0,4198 |
| 7 | 45 | 0,3218 | 7 | 45 | 0,6277 |
| 8 | 55 | 0,4585 | 8 | 55 | 0,8244 |
| 9 | 70 | 0,5465 | 9 | 70 | 1,0727 |
| 10 | 90 | 0,5873 | 10 | 90 | 1,2070 |

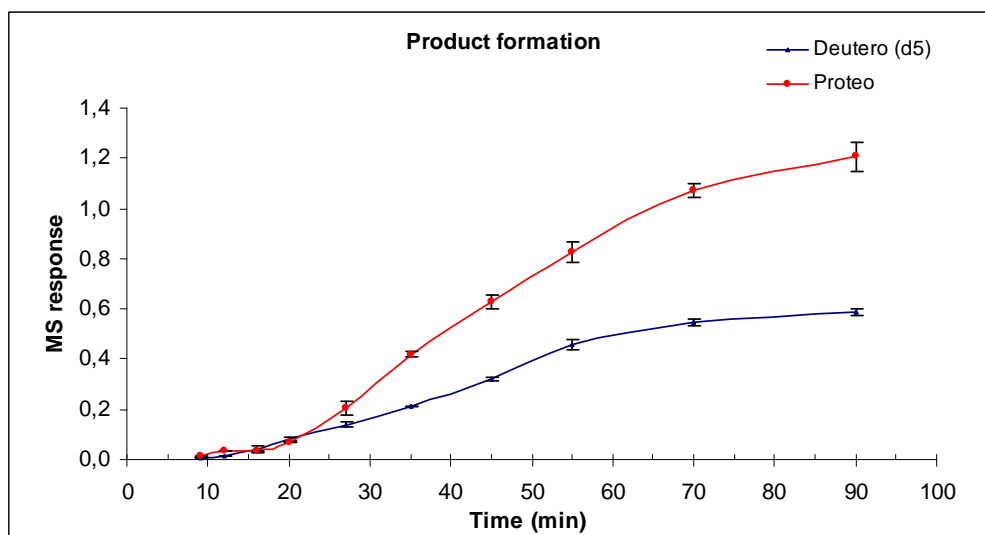


Figure 2.24. Method A: Product formation for proteo and deuterio (d₅) substrates versus time.

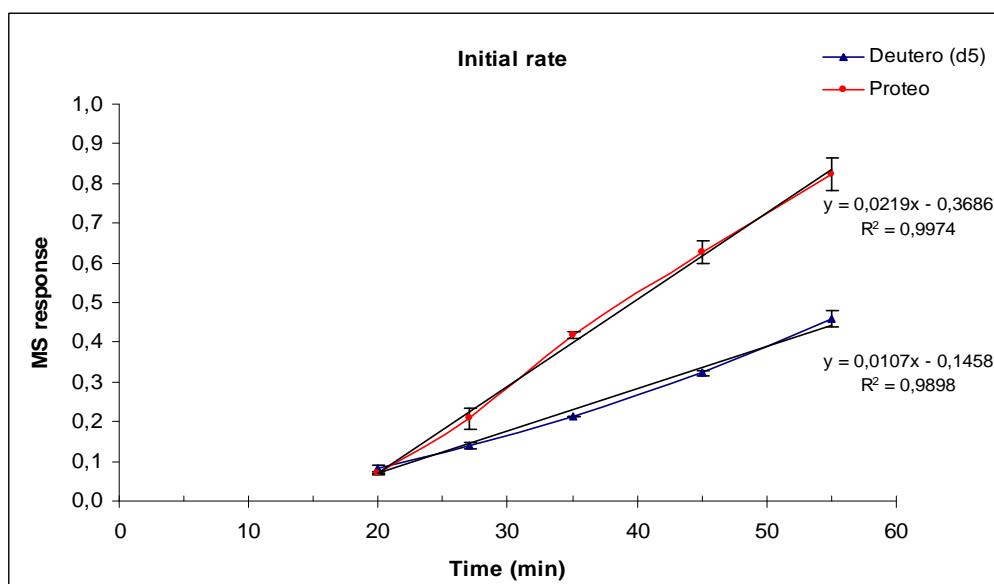


Figure 2.25. Method A: Initial rate of product formation for proteo and deuterio (d₅) substrates.

$$\text{KIE: } k_H / k_D = 0.0219 / 0.0107 = 2.05$$

Method B:

Procedure B was used to determine the initial rate of the reaction.

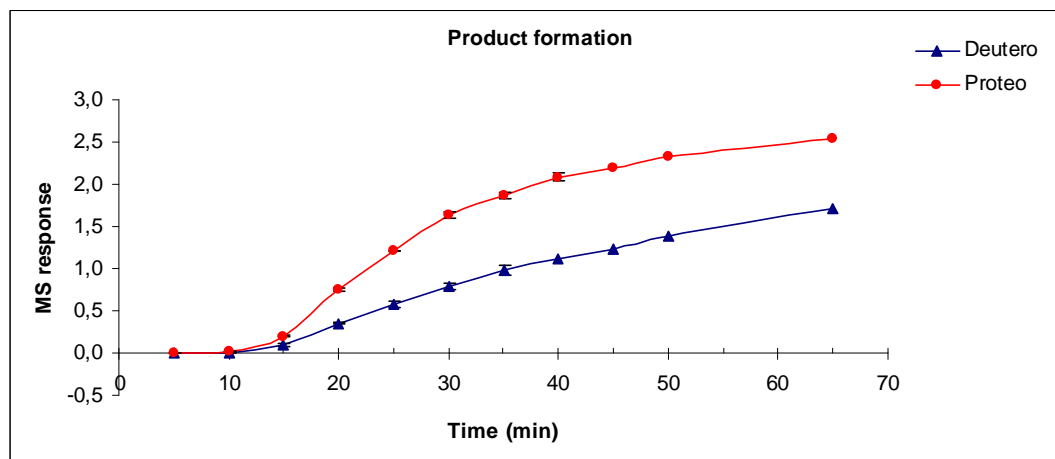


Figure 2.26. Method B: Product formation for proteo and deuterio (d_5) substrates versus time.

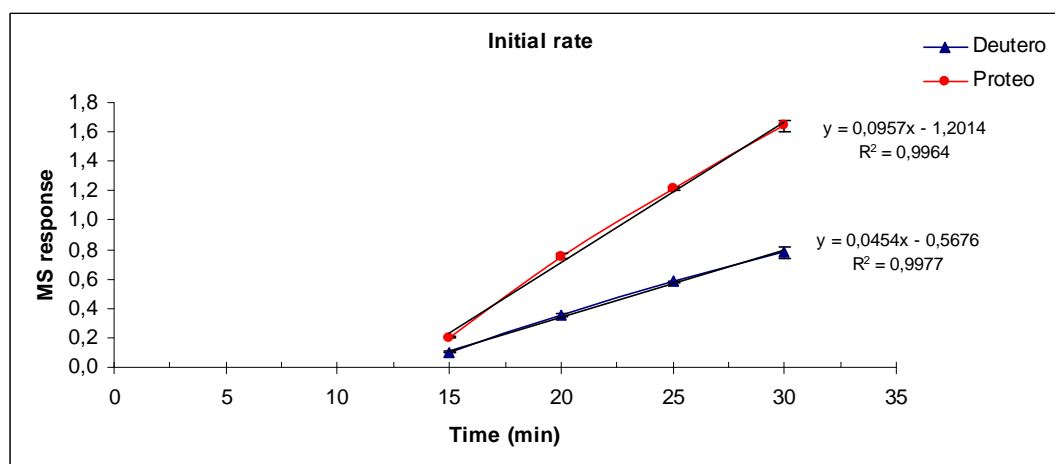
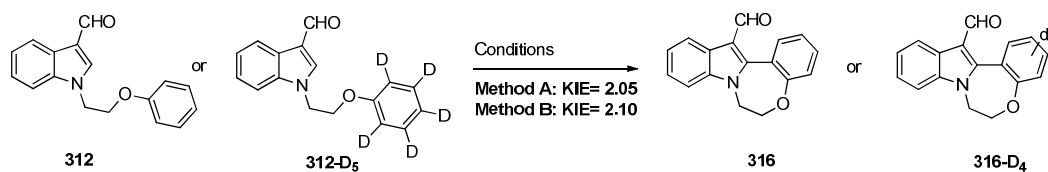


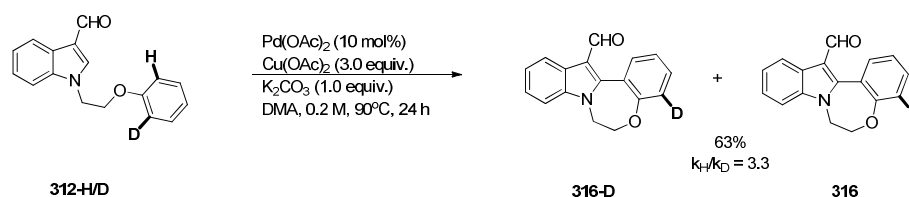
Figure 2.27. Method B: Initial rate of product formation for proteo and deuterio (d_5) substrates.

$$\text{KIE: } k_H / k_D = 0.0957 / 0.0454 = 2.10$$

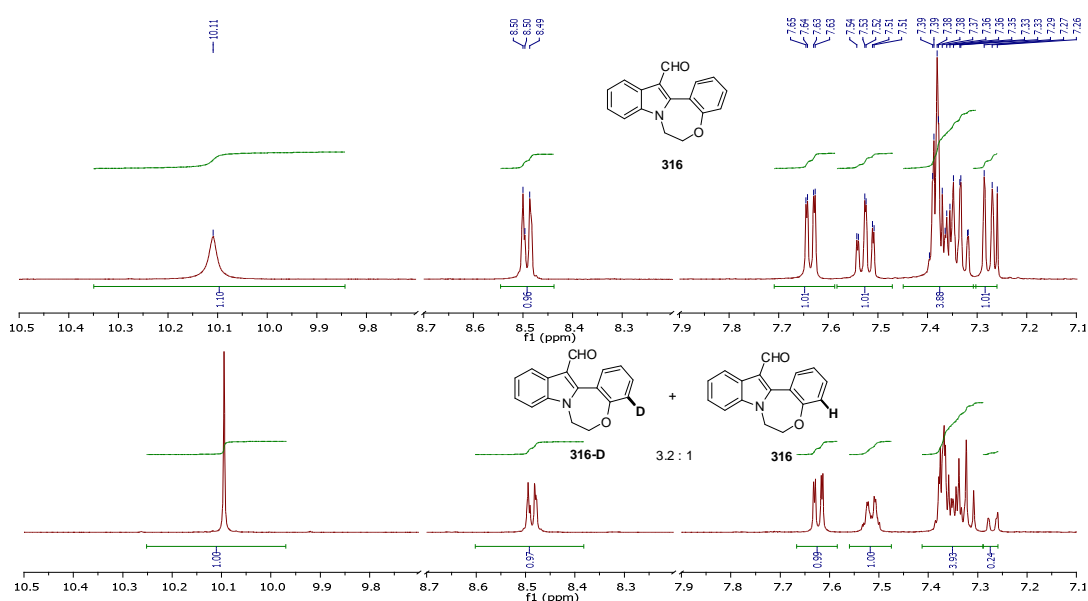
Summary:



2.5.5.2.3 Intramolecular Kinetic Isotope Effects^{128,152}



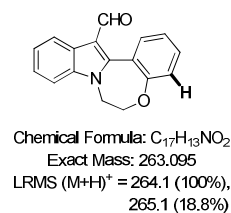
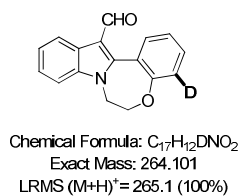
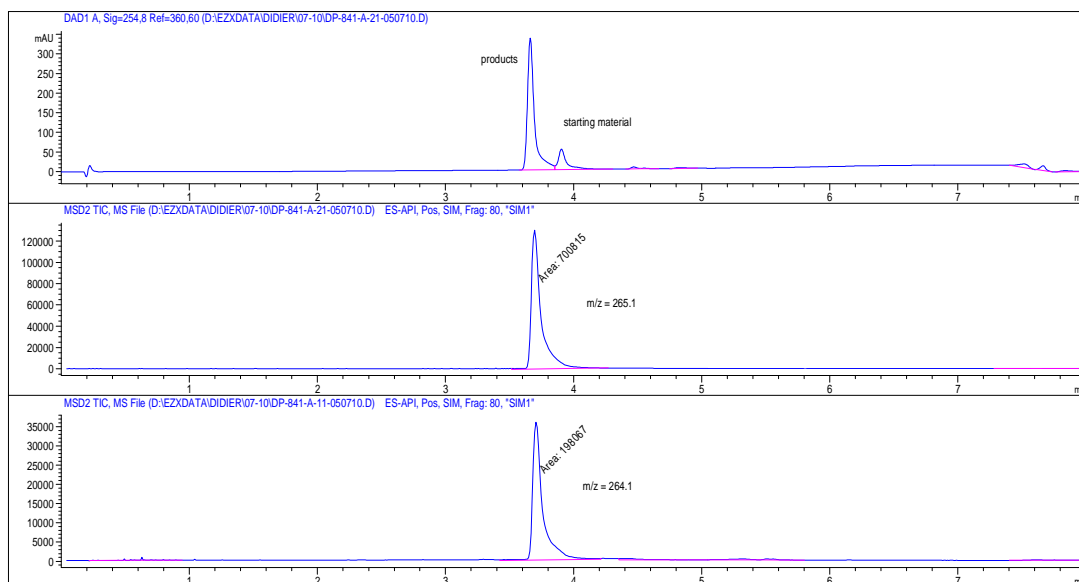
Following our general procedure C, 1-(2-*o*-deuteriophenoxy-ethyl)-1*H*-indole-3-carbaldehyde **312-H/D** (60.0 mg, 0.225 mmol), K₂CO₃ (31.0 mg, 0.225 mmol), Pd(OAc)₂ (5.0 mg, 0.0225 mmol), Cu(OAc)₂ (123.0 mg, 0.675 mmol) and anhydrous DMA (1.5 mL). The tube was then sealed with a serum cap and the reaction was flushed with nitrogen. The reaction mixture was allowed to stir at room temperature until the starting material completely dissolved before being placed into a pre-thermostated carrousel at 90°C for 16 hrs. The mixture was allowed to cool down and directly poured on top of a long silica gel column chromatography. The product was eluted with a mixture hexane/Et₂O (1:1). Pure product was obtained in 63% yield as a white solid. R_f [DCM] = 0.30. ¹H NMR (500 MHz, CDCl₃) δ 10.09 (s, 1H), 8.62 – 8.39 (m, 1H), 7.62 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.42 – 7.29 (m, 4H), 7.27 (dd, *J* = 8.4, 1.2 Hz, 0.24H), 4.62 (t, *J* = 5.7 Hz, 2H), 4.34 (t, *J* = 5.7 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 186.0 (quat), 154.1 (quat), 147.9 (quat), 135.7 (quat), 132.5 (CH), 132.0 (CH), 125.9 (quat), 124.9 (CH), 124.1 (CH), 123.4 (quat), 123.2 (CH), 122.9 (t, *J* = 24.9 Hz, CD), 122.7 (CH), 114.6 (quat), 108.6 (CH), 74.7 (CH₂), 41.5 (CH₂).



Determination of intramolecular kinetic isotope effect by ^1H NMR:

$$k_{\text{H}}/k_{\text{D}} = (1.00 - 0.24)/0.24 = 3.2$$

Determination of intramolecular kinetic isotope effect by LCMS analysis:



| LRMS $(\text{M}+\text{H})^+$ | surface area | corrected surface area ^a |
|------------------------------|--------------|-------------------------------------|
| 264.1 | 198067 | 198067 |
| 265.1 | 700815 | 663474 ^b |

^aCarbon ^{13}C abundance: 1.109%

^bReduced by carbon-isotope signal of [264.1]

$$\text{ESI-MS ratio: } [265.1]/[264.1] = k_{\text{H}}/k_{\text{D}} = 663474/198067 = 3.3$$

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Intramolecular Oxidative C–H Coupling for Medium-Ring Synthesis

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Supporting Information

ABSTRACT: An oxidative C–H coupling is described for medium-ring synthesis.

Transition-metal-catalyzed oxidative C–H coupling offers a highly efficient approach to biaryl synthesis.¹ Using two C–H bonds as coupling partners, no pre-functionalization is required and the reaction can, in principle, afford minimal waste products. The field has undergone rapid growth in recent years, with a number of impressive intermolecular cross-couplings being developed.² The intramolecular variant, by contrast, has not been widely investigated. Seminal work in the 1970s established the reaction for five-membered, fully aromatic systems such as carbazoles and dibenzofurans,^{3,4} but applications to alternative ring systems are rare (Figure 1). We reasoned that dehydrogenative coupling for the synthesis of medium-ring-containing biaryls would represent a powerful approach to these compounds, which are often difficult to access by classical routes. These challenges are particularly relevant to medicinal chemistry; despite the plethora of medium-ring structures found in biologically active natural products, seven-, eight-, and nine-membered rings remain rare in drug molecules (Figure 1).⁵

We chose to study the indole system, given its widespread occurrence in biologically active compounds.⁶ A screen of *N*-alkylated indoles identified compounds of general structure **1**, containing an electron-withdrawing group (EWG) at the indole 3-position, as potential substrates for dehydrogenative seven-membered ring formation. A catalyst optimization study (Supporting Information) established that catalytic Pd(OAc)₂ in the presence of excess Cu(OAc)₂, using DMA as solvent, was effective for C–C bond formation, with the parent structure **2a** being formed in 77% yield (Chart 1). With these conditions in hand, we examined their generality for seven-membered ring formation. A range of indole substrates corresponding to general structure **1** were prepared, whereby the substituent pattern, heteroatom substitution, and EWG at the indole 3-position were all varied.

We were pleased to see that the reaction conditions proved general, delivering a variety of medium-ring annulated indoles in good to excellent yield.⁷ Aromatic rings containing *p*-MeO and *p*-CF₃ groups were good substrates for the reaction, affording indoles **2b** and **2c** in 60 and 80% yields, respectively. A substrate containing a *m*-fluoro aromatic ring was prepared to gain some insight into the mechanism of the reaction. Medium-ring biaryl **2d** was formed as the major regioisomer (63% overall yield, 4:1 dr), i.e., the more acidic hydrogen atom⁸ underwent reaction, suggesting a base-assisted palladation pathway was operating in the reaction mechanism (*vide infra*). Incorporation of heteroatoms into the

Dehydrogenative arylation

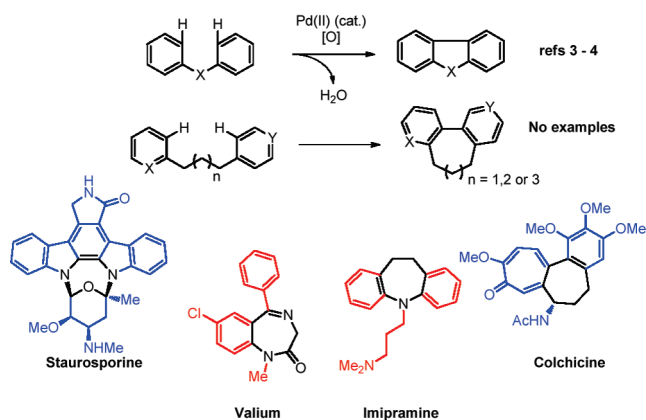


Figure 1. Dehydrogenative coupling for medium-ring biaryl synthesis. Examples of biologically active medium-ring containing biaryls from Nature (blue) and pharmaceuticals (red).

tethering chain was possible, with the three oxazapane derivatives **2e**, **2f**, and **2g** all formed in good yield.

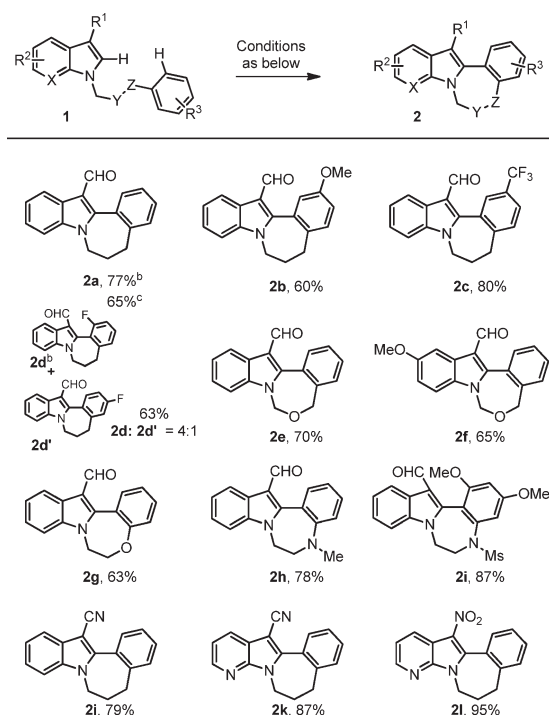
Interestingly, no five-membered ring products from C–H activation at the benzylic position were observed for substrates **2e** and **2f**, despite the susceptibility of benzyl ethers to oxidation.⁹ *sp*² C–H activation to form the medium ring is evidently favored under these reaction conditions. Nitrogen substitution into the medium ring was likewise possible, with the diazapane analogues **2h** (NMe) and **2i** (NMs) being formed in very good yield. A good EWG at the indole C3 was necessary for reaction, with esters and ketones producing low yields of medium-ring product (Supporting Information). The cyano group was proficient, however, affording annulated indole **2j** and the azaindole **2k** in high yield. The nitro group proved the most effective of all, enabling the azaindole **2l** to oxidatively couple in an excellent 95% yield.

We extended the work to encompass heteroaromatic ring systems, with the aim of synthesizing novel heterobiaryls annulated in a seven-membered ring (Chart 2). The reaction was very effective for the synthesis of symmetrical bisindole **4a**, synthesized in 91% yield from C2 oxidative coupling of the symmetrical precursor. We could likewise use both benzimidazole and pyrazole C–H bonds as participants in the reaction to form the highly functionalized biheteroaryls **4b**, **4c**, and **4d** in good yields.

Following the success of the reaction for seven-membered ring synthesis, we applied the same approach to the more challenging

Received: October 9, 2010

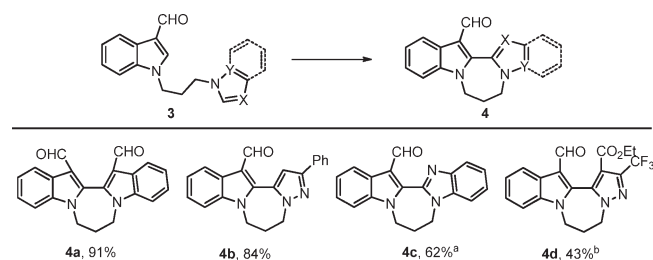
Published: December 31, 2010

Chart 1. Scope of Oxidative Coupling of Indole with Arenes To Form Annulated Seven-Membered Rings^a

^a Reaction conditions: 0.2 mmol of the substrate, 10 mol % Pd(OAc)₂ (0.02 mmol), K₂CO₃ (0.2 mmol), Cu(OAc)₂ (0.6 mmol) in 1 mL of DMA at 90 °C for 16 h. Isolated yields throughout.

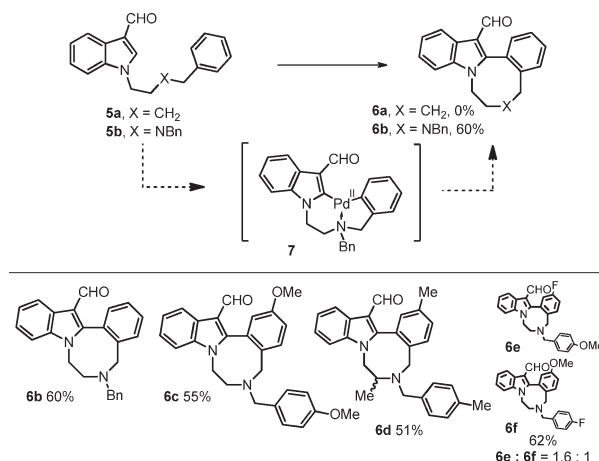
^b Crystallographic data available.

^c Reaction conditions: 2.0 mmol of 1a, 10 mol % Pd(OAc)₂ (0.2 mmol), K₂CO₃ (2.0 mmol), Cu(OAc)₂ (6.0 mmol) in 10 mL of DMA at 90 °C for 16 h.

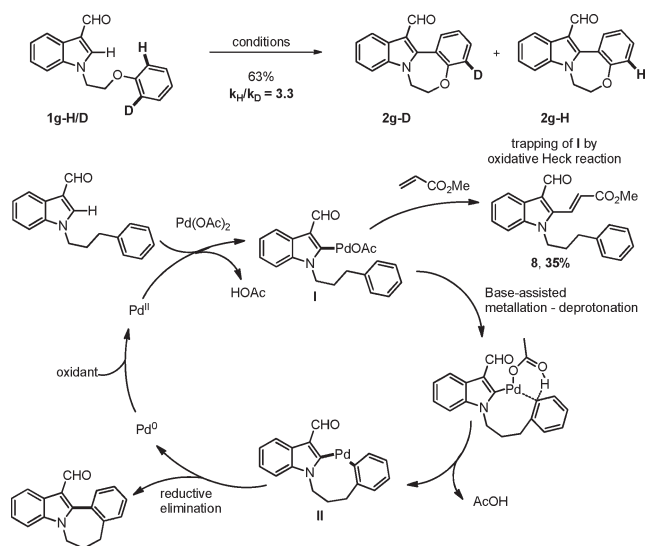
Chart 2. Intramolecular Oxidative Coupling of Indole and Heteroarenes^a

^a Reaction conditions: 0.2 mmol of the substrate, 10 mol % Pd(OAc)₂, K₂CO₃ (0.2 mmol), Cu(OAc)₂ (0.6 mmol) in 1 mL of DMA at 120 °C for 8 h. Isolated yields throughout. Exceptions: ^a140 °C for 3 h. ^b120 °C for 24 h.

eight-membered -ring targets (Chart 3). Eight-membered rings are generally the most difficult of the medium rings to form, due to energetically unfavorable transannular and torsional strain effects in ring-closing reactions.¹⁰ These difficulties were manifest in our initial attempts at oxidative cyclization of substrate 5a, which were unsuccessful under a range of conditions. We reasoned that the replacement of a methylene in the tethering chain with a heteroatom might serve to both reduce transannular strain and provide a stabilizing interaction with the presumed

Chart 3. Formation of Eight-Membered Rings by Dehydrogenative Coupling^a

^a Reaction conditions: 0.2 mmol of the substrate, 10 mol % Pd(OAc)₂, K₂CO₃ (0.2 mmol), Cu(OAc)₂ (0.6 mmol) in 1 mL of DMA at 120 °C for 16 h.

Scheme 1. Mechanistic Studies^a

^a Reaction conditions for KIE study: indole (0.225 mmol), K₂CO₃ (0.225 mmol), Pd(OAc)₂ (0.0225 mmol), Cu(OAc)₂ (0.675 mmol) in 1.5 mL of DMA at 90 °C for 16 h. *k_H*/*k_D* determined by ¹H NMR and LRMS.

Pd(II) intermediate in the reaction (structure 7).¹¹ We were pleased to see that incorporation of a dibenzylamine group (5b) into the substrate proved a success, providing eight-membered diazocane derivative 6b in 60% yield. This reaction was extended to a small range of examples: Products 6b and 6c arise from dibenzylamine derivatives containing four identical sites for aromatic C–H activation. Interestingly, 6d was isolated as a 1:1 mixture of diastereoisomers, suggesting hindered rotation around the biaryl axis. The dibenzyl motif allowed us to set up a competition experiment to probe the mechanism, using electron-rich (*p*-OMe) and electron-poor (*p*-F) benzyl groups in the same substrate. Compounds 6e and 6f were isolated in 62% combined

yield in the ratio 1.6:1. The more acidic C–H bond on the fluoro-substituted arene is preferentially activated, although the selectivity is reduced relative to that seen with the previous seven-membered systems (Chart 1, **2d** and **2d'**).

A preliminary picture of the reaction mechanism is set out in Scheme 1. Palladation of the indole at C2 forms complex I, an intermediate that could be successfully trapped with methyl acrylate in a Fujiwara–Moritani-type process¹² to give ester **8** (Supporting Information). In the normal course of reaction, I then undergoes a concerted metalation–deprotonation (CMD)¹³ step to afford intermediate II. An alternative electrophilic palladation mechanism is unlikely here due to the observed selectivities for electron-poor sites in competition experiments (**2d** in Chart 1 and **6g/6f** in Chart 3).¹⁴ In addition, an intramolecular kinetic isotope effect (KIE) study on substrate **1g**-H/D gave a value of $k_{\text{H}}/k_{\text{D}} = 3.3$, in line with literature reports of C–H activation via CMD mechanisms.^{4c,15,16} Reductive elimination then produces the medium-ring products, along with Pd(0) which is reoxidized by the excess Cu(II) in the reaction.

In conclusion, we have shown for the first time that intramolecular oxidative C–H coupling is an effective strategy for synthesizing medium-ring compounds. The reaction is tolerant of a rich array of functional groups, forming annulated heterocycles for application as versatile scaffolds in medicinal chemistry^{17,18} Previous routes to these medium-ring-containing indoles have featured lengthy, multistep routes; our approach is rapid, using a simple catalyst system, and should be amenable to a broad range of further applications in medium-ring heterocycle synthesis.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedures and characterization data for all new compounds (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ ACKNOWLEDGMENT

We thank the EPSRC and the University of Edinburgh for funding (Leadership fellowship to M.F.G. and studentship to D.G.P.) and the EPSRC mass spectrometry service at Swansea. Dr. Fraser White is thanked for X-ray crystallography.

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